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**The Effects of Superior Olivary Complex Lesions on
Binaural Interaction in the Inferior Colliculus of the Albino
Rat**

by

Sharon Louise Sally, 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, 1990

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The Effects of Superior Olivary Complex Lesions on Binaural
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submitted by Sharon Louise Sally, B.A.

in partial fulfilment of the requirements for
the degree of Master of Science

Thesis Supervisor

Chair, Department of Psychology

Carleton University

April, 1990

Abstract

Cells in the superior olivary complex of the adult albino rat were selectively destroyed by micro-injections of kainic acid. Following a recovery period of approximately one month, the binaural response properties of cells in the inferior colliculus were examined using microelectrode recording techniques. Both summation and suppression binaural responses were found in animals with unilateral and bilateral lesions of the SOC. Interaural intensity difference (IID) sensitivity was assessed by comparing near threshold contralateral intensity with the lowest ipsilateral intensity which unequivocally produced a summation or suppression response. Interaction IIDs for animals with unilateral SOC lesions did not differ from those previously obtained in normal rats; however, IIDs for the bilateral lesion cases differed significantly. Modal IID values for bilateral lesion cases were elevated in comparison with normals. Thus, binaural interactions were affected but not eliminated by bilateral destruction of the SOC.

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INTRODUCTION

The following review will focus upon some of the neuronal mechanisms which enable animals to localize sounds in space. This work will rely heavily upon research concerning the auditory system in the cat since this species has been studied extensively. Auditory processing in the rat will be considered in light of the evidence obtained from the cat as well as other mammalian species so that cross species comparisons can be made.

The ability to localize sounds in space is largely dependent upon the fact that a sound located laterally in space reaches the ear closest to the sound source first due to the greater distance to the contralateral (far) ear. Moreover, the sound is more intense at the ipsilateral (near) ear due to a shadowing effect of the head. When the wavelength of the sound is smaller than the size of the head, the head creates a sound shadow thus decreasing the intensity of the sound at the contralateral ear. Differences in time of arrival and intensity of the sounds at the two ears are termed interaural time and intensity cues respectively. Both of these cues enable the listener to localize sounds in space. This review will focus upon the neuronal processing of interaural intensity differences (IIDs) in the mammalian brainstem and midbrain.

The Superior Olivary Complex

Input from each ear is transmitted via the auditory nerve on each side from the cochlea to the cochlear nucleus and is subsequently relayed to the superior olivary complex (SOC). The SOC is the lowest centre in the central auditory pathway which receives input from the two ears and is thus strategically located in the brainstem for processing binaural time and intensity cues. The SOC is comprised of a number of closely associated nuclei located in the lateral part of the ventral pons. The SOC has been most extensively investigated in the cat and will thus be first described. The major nuclei of the SOC are the superior olive proper, usually referred to as the lateral superior olivary nucleus (LSO); the accessory, or medial superior olivary nucleus (MSO) and the medial nucleus of the trapezoid body (MNTB). The LSO, the most conspicuous of these in Nissl-stained material, is seen as an S-shaped nucleus in coronal sections. The MSO is a curved-band of spindle-shaped cells located medial to the LSO. The third cell group, lying within the fibers of the trapezoid body, ventromedial to the MSO, is the MNTB. A number of smaller and less clearly defined nuclei are also present within the SOC. Ventral to the MNTB and the LSO respectively, are nuclei termed ventral and lateral nuclei of the trapezoid body (VTB and LTB). In addition, a group of nuclei collectively referred to as periolivary nuclei are located at the margins of the SOC. There is an absence of clear nuclear boundaries in this region. The major nuclei of the SOC (LSO, MSO and MNTB) have been studied extensively in

terms of binaural processing, as the LSO and MSO gain afferents from both ears (via the cochlear nucleus) and the MNTB supplies contralateral afferents to the LSO. The SOC of the rat and other mammals is also comprised of these major nuclei although species differences exist in the relative sizes of these nuclei (Harrison and Feldman, 1970; Harrison and Irvine, 1966; Irvine and Harrison, 1967). Relative to other mammals, those with high frequency hearing (eg. rat, mouse, hedgehog and dolphin) have an MSO which is small or absent while the MNTB and LSO in these species are relatively large (Harrison and Howe, 1974; Irving and Harrison, 1967). However, despite variation in the relative sizes of the major nuclei, the cellular morphology and connections are similar to the cat across a broad range of mammalian species (eg. rat: Harrison and Warr, 1962, Harrison and Feldman, 1970 dog: Goldberg and Brown, 1968; rabbit: Borg, 1973; kangaroo rat: Browner and Webster, 1975; mouse: Ollo and Schwartz, 1979; Willard and Ryugo, 1983; echolocating bats: Schweitzer, 1981; Zook and Casseday, 1982). In addition to the major nuclei of the SOC, the SOC of the rat (Beyerl, 1978; Coleman and Clerici, 1987; Druga and Syka, 1984), mouse (Ollo and Schwartz, 1979; Willard and Ryugo, 1983), gerbil (Nordeen et al., 1983) and opossum (Willard and Martin, 1983) also contains a large nucleus termed the superior paraolivary nucleus (SPO) which is absent in the cat. This nucleus is situated dorsomedially to the small MSO. Binaural processing in this nucleus has not been described.

Medial Nucleus of the Trapezoid Body.

The principal cells of MNTB receive a topographically organized projection from the ventral division of the contralateral cochlear nucleus (Harrison and Feldman, 1970; Harrison and Warr, 1962; Warr, 1972). Consequently, the principal cells of MNTB are tonotopically organized, with high-to-low characteristic frequencies (CF=frequency to which the neuron responds at threshold) arranged in a ventromedial-to-dorsolateral direction (Guinan et al., 1972a,b). There is a disproportionately large representation of higher frequencies in this nucleus due to a lower cell density in the dorsolateral part of the nucleus (Guinan et al., 1972 a,b). The principal cells appear to be the only cells of the MNTB exhibiting tonotopic organization (Guinan et al., 1972a,b). 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., 1972 a,b). The principal cells of MNTB receive large axosomatic calyces of Held which stem from the large fibers within the trapezoid body. Each calyx is a cup-shaped expansion of the axon which extends over the surface of the principal cell with finger-like processes (Jean-Baptist and Morest, 1975; Morest, 1968). The calyx forms a secure synapse with the principal cells of MNTB. 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 transmission by large-diameter fibers and calyceal terminals.

Anterograde degeneration studies in the cat (van Noort, 1969; Rasmussen, 1967) rabbit (Borg, 1973) and kangaroo rat (Browner and Webster, 1975) indicate that the cells of MNTB project to the LSO of the same side. Anterograde tracer studies indicate a topographically organized projection to the LSO which is dense to all parts of the nucleus except the lateral limb (Elverland, 1978; Glendenning et al., 1985). The MNTB also sends an ascending projection to the intermediate nucleus of the lateral lemniscus. (Glendenning et al., 1981). However, the function of this nucleus beyond its role as a relay station between the CN and the LSO is not yet known.

Lateral Superior Olivary Nucleus.

The LSO receives ipsilateral input via the trapezoid body from the ventral division of the cochlear nucleus (VCN) (Harrison and Warr, 1962; Stotler, 1953; Warr, 1966) and receives contralateral input from the cells in the VCN which reach the LSO indirectly via the principal cells of MNTB. For the majority of neurons in the LSO the ipsilateral afferents to the LSO are excitatory, while the contralateral afferents (via MNTB) are inhibitory. The response characteristics of the LSO cells are thus termed "IE"-ipsilateral monaural stimulation excites, contralateral monaural stimulation

inhibits¹. For these cells stimulation of the contralateral ear inhibits the response to ipsilateral ear stimulation (Boudreau and Tsuchitani, 1968, 1970; Guinan et al., 1972, Tsuchitani, 1977). The remaining cells also receive ipsilateral excitatory input, with the contralateral ear generally having no effect (OE) (Guinan et al., 1972 a,b; Tsuchitani, 1977). 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). For any one cell 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). The frequency specific convergence of ipsilateral and contralateral input

¹ Although various schemes have been used to classify binaural response types, a two-letter code will be used in the introduction and discussion of this paper. The first letter indicates response to monaural stimulation of the contralateral ear, while the second letter designates the response to ipsilateral monaural stimulation.

enables the cells of the LSO to analyze the intensity difference of the sound stimulus reaching the two ears. Each LSO subtracts the sound spectrum reaching its contralateral ear from the spectrum reaching its ipsilateral ear (Boudreau and Tsuchitani, 1970). Thus, the number of discharges evoked in a neuron in the LSO is due to the level of excitatory drive from the ipsilateral ear and the level of inhibitory drive from the contralateral ear. In the cat (Adams, 1979; Brunso-Bechtold et al, 1981; Roth et al., 1978; Stotler, 1953), rat (Beyerl, 1978; Coleman and Clerici, 1987), opossum (Willard and Martin, 1983), kangaroo rat (Browner and Webster, 1975) and bat (Zook and Casseday, 1982) the LSO has been shown to project bilaterally to the inferior colliculus (IC). Bilateral projections of the LSO to the dorsal nucleus of the lateral lemniscus (DNLL) have also been noted in the cat (Elverland, 1978; Glendenning et al., 1981).

The arrangement of projections from the LSO to the IC in the cat has been described using a range of tract-tracing techniques (Glendenning and Masterton, 1983). Cells projecting ipsilaterally are concentrated in the lateral limb of the LSO, while those projecting contralaterally are concentrated in the medial limb. Only a small proportion (less than 5%) are shown by retrograde double labelling experiments to project bilaterally via axon collaterals (Glendenning et al., 1983). In accordance with these findings, Schneiderman and Henkel (1987) have recently demonstrated that the cells in the lateral limb of the LSO distribute axons over larger

areas in the contralateral than ipsilateral IC, whereas cells in the medial limb project to larger areas in the ipsilateral IC. In contrast to these studies, retrograde labelling experiments in the rat appear to indicate that the projections of the LSO to the ipsilateral and contralateral IC arise from cells which are more homogeneously distributed throughout the nucleus (Beyerl, 1978).

Medial Superior Olivary Nucleus.

The MSO receives bilateral projections from the VCN. Degeneration studies at the light microscopic level in the cat (Stotler, 1953; Warr, 1966; van Noort, 1969), rat (Harrison and Irvine, 1966), dog (Goldberg and Brown, 1968), and rhesus monkey (Strominger and Strominger, 1971) have shown that axons from the contralateral and ipsilateral VCN terminate on the medial and lateral dendrites, respectively, of cells in the MSO. The large majority of MSO neurons are responsive to stimulation of either ear. In the cat and dog, about 75% of the units are excited by stimulation of either ear alone and are thus termed "EE" cells (Goldberg and Brown, 1968; Guinan et al., 1972a,b). In the dog, the remaining neurons are EI (15.2%), the converse, IE (8.6%) or E0 (10.5%). Proportions which differ somewhat from these have been reported in the rat. Inbody and Feng (1981) reported that EE cells comprised 52% and EI cells 48% of the sample. It has been suggested that this proportional shift may be unique to animals with high frequency hearing and less well developed MSOs (Irvine, 1986). The MSO is

tonotopically organized with low CFs located dorsally and high CFs located ventrally. For most of the binaurally responsive neurons in the cat (Guinan et al., 1972a,b), rat (Inbody and Feng, 1981), and dog (Goldberg and Brown, 1969) the CFs and response areas determined for each ear are similar. In both the cat and dog there is a disproportionately large representation of low frequencies in MSO, the majority of units having CFs below 4 kHz and very few units having CFs greater than 11 kHz (Goldberg and Brown, 1969; Guinan et al., 1972a,b). Similarly, in the rat, only low frequency neurons have been isolated (Inbody and Feng, 1981).

Degeneration studies in the cat (van Noort, 1969; Stotler, 1953) and kangaroo rat (Browner and Webster, 1975) and tracer studies in the cat (Adams, 1979; Aitkin and Schuck, 1985; Brunso-Bechtold et al., 1981; Elverland, 1978; Glendenning and Masterton, 1983; Henkel and Spangler, 1983; Roth et al., 1978) rat (Beyerl, 1978; Coleman and Clerici, 1987) and bat (Zook and Casseday, 1982) indicate that the MSO has ascending projections to the ipsilateral IC. Ascending projections to the ipsilateral DNLL have also been reported in the cat (Elverland, 1978; Glendenning et al., 1981).

Processing of Interaural Intensity Differences in the Superior Olivary Complex.

Goldberg and Brown's (1969) observations on the sensitivity of dog MSO cells to interaural time and intensity differences laid the foundation toward an understanding of spatial processing in the SOC.

These investigators found that a distinction could be made between different classes of binaurally responsive neurons. EE cells are relatively insensitive to interaural intensity change, as long as the average intensity remains constant. A decrease in the response of the neuron to attenuation of the sound at one ear is partially offset by an increase in responsiveness to the augmented sound at the other ear. Although the compensation is not perfect, the discharge rate of these neurons is primarily determined by average binaural intensity level. Conversely, EI or IE cells are more sensitive to interaural intensity changes than to average binaural intensity change. If the overall intensity of a sound is increased, the increased excitatory input to one side will be partially offset by an increase in inhibitory input. Interaural intensity changes, however, will cause large changes in the response of these neurons.

The general sensitivity of EI/IE cells to IID have been demonstrated in studies of the LSO of the cat (Boudreau and Tsuchitani, 1968, 1970; Caird and Klinke, 1983; Hall, 1965; Tsuchitani and Boudreau, 1969) and bat (Harnischfeger et al., 1985) and MSO of the rat (Inbody and Feng, 1981). The discharge rate of an EI neuron to excitatory contralateral stimulation progressively declines as the intensity of the ipsilateral inhibitory stimulus is increased. When the intensity at the ipsilateral ear equals or exceeds that at the contralateral ear, the neural activity of EI neurons is generally completely suppressed.

Inferior Colliculus

All major nuclei of the SOC project either directly to the IC via the fibers of the lateral lemniscus or indirectly by synapsing on cells of the nuclei of the lateral lemniscus which in turn project to the IC (Aitkin and Phillips, 1984; Goldberg and Moore, 1967). The central nucleus of the IC (ICC) is a centrally located mass of densely packed neurons surrounded by a layer of cells which has been divided into a pericentral nucleus (ICP) covering the dorsal and posterior surfaces of the ICC, and an external nucleus (ICX), that covers the lateral and anterior surfaces. Retrograde tracing studies have indicated that the ICC is the site of termination for most of the projections from brainstem auditory nuclei. Large injections of horseradish peroxidase (HRP) into the ICC in the cat (Adams, 1979; Brunso-Bechtold et al., Roth et al., 1978), rat (Beyerl, 1978; Coleman and Clerici, 1987; Druga and Syka, 1984a), mouse (Ryugo et al., 1981; Willard and Ryugo 1983), gerbil (Nordeen et al., 1983), brush-tailed possum (Aitkin and Kenyon, 1981) and bat (Schweitzer, 1981; Zook and Casseday, 1982) result in large numbers of labelled neurons in the LSO bilaterally and the MSO ipsilaterally. In the cat, evidence from degeneration and axonal tracer studies indicates that projections to the ICC from almost all brainstem nuclei are topographically organized (Adams, 1979; Brunso-Bechtold et al., 1981; Henkel and Spangler, 1981; van Noort, 1969; Oliver, 1984, Osen, 1972; Roth et al., 1978). The topographic projection from the LSO has been described for the rat (Beyerl, 1978). Projections to

the dorsal part of the central nucleus arise from neurons in the low-frequency regions of brainstem structures, while projections to ventral ICC derive from neurons in the high-frequency region of these nuclei. This topographic organization of projections concurs with the physiological evidence of a dorsal-to-ventral, low-to-high frequency organization in the ICC. Physiological evidence of a single cochlear representation in the ICC indicates a highly organized projection of afferents from multiple brainstem sources.

The ICC projects in a topographically organized fashion, to the ventral division of the medial geniculate body, which is the major source of input to primary auditory cortex and to the other tonotopic cortical fields (see Imig and Morel, 1983 for review of thalamocortical auditory system).

Frequency Tuning and Tonotopic Organization.

Tuning curves are obtained by measuring the intensity necessary to elicit a threshold response at different frequencies along the auditory range. In the cat the majority of neurons in the ICC respond to a restricted range of frequencies near their threshold and thus have 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, in the cat, the tuning curves of most neurons in ICX (Aitkin et al, 1975; 1978b) and in ICP (Aitkin et al., 1975; Merzenich and Reid, 1974) are broad and irregular often extending over several octaves. Similarly,

in the rat, neurons in peripheral regions of IC 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. 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). Sharp frequency tuning and dorsal-to-ventral tonotopic organization has also been shown to be characteristic of the ICC in the rat (Clopton and Winfield, 1973; Flammino and Clopton, 1975; Kelly, Glenn and Beaver, in preparation), rhesus monkey (Ryan and Miller, 1978), squirrel monkey (Fitzpatrick, 1975), rabbit (Aitkin et al., 1972a; Syka et al., 1981), guinea pig (Popelar and Syka, 1982), brushtailed possum (Aitkin et al., 1978a), mouse (Harnischfeger, 1978; Willott and Urban, 1978) and bat (Grinnell, 1963; Jen and Schlegel, 1982; Vater et al., 1979). Tonotopic organization is difficult to discriminate in ICX and ICP because broad tuning of neurons in this region precludes accurate determination of CFs.

Binaural Response Properties.

Binaural interaction patterns at the IC are similar to those seen in nuclei of the SOC. At the IC, however, almost all neurons receive excitatory input from the contralateral ear. The proportions of the major binaural interaction types have been examined extensively in the ICC of the cat. Three studies (Aitkin et al., 1975;

Roth et al., 1978; Semple and Aitkin, 1978) have presented data from large samples of neurons with CFs covering the audible frequency range. A significant proportion (17-24%) of neurons were excited by stimulation of the contralateral ear, but uninfluenced by ipsilateral stimulation (EO). A slightly larger proportion of cells (30-38%) received EI input and were sensitive to IIDs. Neurons which exhibited an increase in response to stimulation of either ear (EE cells) or increased responsiveness to stimulation of both ears comprised 33-48% of the population. While estimates vary concerning the proportions of binaural interaction types in the ICC of the rat, all studies have reported that EI interactions were in the majority (Flammino and Clopton, 1975; Kelly, Glenn and Beaver, in preparation; Silverman and Clopton, 1977; Skya, Popelar and Druga, 1983).

In the ICC of the cat, binaural response type is related to the CF of neurons. EE cells more commonly have low than high CFs (Kuwada and Yin, 1983; Rose et al., 1966; Semple and Aitkin, 1979). Conversely, EO and EI patterns occur more frequently in cells above 3-5 kHz (Roth et al., 1978; Semple and Aitkin, 1979). Recent evidence suggests that there is also a partial segregation of binaural classes in the ICC beyond that which is consequent on frequency organization. Within the ICC of the cat, EI cells are encountered in greatest proportion rostrally and EO cells are encountered in greatest proportion caudally and laterally (Roth et al., 1978; Semple and Aitkin, 1979). There is also some evidence in

the cat and bat ICC that there may be a partial segregation of major binaural response types within laminae of neurons sharing common CFs. (Roth et al., 1978; Semple and Aitkin, 1979; Wenstrup et al., 1985).

Coding of Interaural Intensity Differences in the Inferior Colliculus.

Studies of ICC neurons in the cat have confirmed that cells receiving EI binaural input are the major class of neurons which exhibit sensitivity to IIDs (Geisler et al., 1969; Hind et al., 1963; Moore and Irvine, 1981; Rose et al., 1963; Semple and Aitkin, 1979). The response of EI neurons to IIDs at the IC parallels the response of these neurons in the auditory brainstem. IID functions are generated by presenting a contralateral tone of a fixed intensity level to a neuron and increasing the level of a simultaneously presented ipsilateral tone in 5 or 10 dB steps. Both the ipsilateral and contralateral tone are presented at the CF of the neuron. For any given stimulus level presented to the contralateral (excitatory) ear, the response rate of the neuron declines as the level of stimulus to the ipsilateral (inhibitory) ear is augmented. Although the IID functions for all EI cells have the same basic form, the IID value at which the response begins to decline as well as the steepness of the function (amount of decline per unit change in ipsilateral SPL) differ between individual neurons. The characteristic form of this IID sensitivity has been confirmed in a number of mammals: rat

(Silverman and Clopton, 1977; Syka et al., 1983), kangaroo rat (Stillman, 1972), rabbit (Aitkin et al. 1972b), guinea pig (Popelar and Syka, 1982), brushtailed possum (Aitkin et al., 1978), and bat (Harnischfeger, 1980; Harnischfeger et al., 1985; Wenstrup et al., 1985).

Wenstrup and co-workers (1985) have reported an orderly arrangement of cells in terms of IID sensitivity in the ICC of the mustache bat. The cells sensitive to IIDs are systematically arranged within a lamina of neurons with common CFs. Within this lamina, there is a progression of cells from those which are sensitive to small differences in interaural intensity to cells whose discharge rates are only affected by larger interaural intensity differences. This organization is likely to play a role in neural representation of the azimuthal location of a sound. This organization has not been described in the IC of other mammals. However, a similar organization of IID sensitivity has been reported to exist in the cat's superior colliculus (Wise and Irvine, 1985).

Proposed Research

Previous research in our laboratory (Kelly, Glenn and Beaver, in preparation) has indicated that the IC of the rat is similar to the cat and other mammals in terms of tonotopic organization and binaural response properties. In the present study we will examine the effects of unilateral and bilateral lesions of the SOC on binaural interactions at the level of the inferior colliculus. This study will

be the first to examine electrophysiologically the contribution of the SOC to binaural integration.

METHODS

Animal Preparation

Experiments were conducted on 11 male Wistar albino rats (Rattus norvegicus) obtained from Charles River Canada Inc., St. Constant, Quebec. Electrophysiological data are presented for 9 animals which received the most complete lesions of the SOC. 6 rats received unilateral lesions of the SOC and 3 received bilateral SOC lesions. Surgical anesthesia was induced with Equithesin (3 ml/kg ip). Equithesin, obtained by us from Jensen-Salsbery Labs, is no longer commercially available. However, a 500-ml aqueous solution containing 21.3 g chloral hydrate, 10.6 g magnesium sulphate, and 4.8 g pentobarbital sodium may be used instead. The animal was placed in a stereotaxic instrument which left the ears unobstructed in order to prevent damage to the tympanic membrane. Kainic acid (1mg/ml) was used to perform unilateral and bilateral lesions of the superior olivary complex. The animals were given atropine sulphate (0.05 mg/kg) prior to surgery to prevent respiratory distress. Following a midline incision, a small hole was drilled in the skull 2.5 mm caudal to bregma and the SOC was approached at an angle to avoid contact with the sinus. 7.5 nmoles (1.5 ul) of kainic acid was injected into the SOC at the rate of 1.5 nmoles per minute. The cannula was then left in place for 5 minutes to allow diffusion of the kainic acid into the surrounding tissues. The animal was given diazepam (4.5 mg/kg) approximately 45

minutes following surgery to prevent generalized seizure activity. Following a recovery period of approximately one month the animal was surgically prepared for recording from the inferior colliculus. Immediately before surgery the external ears and tympanic membranes were examined with an otoscope and determined to be free of disease or obstruction. Surgical anesthesia was induced with Equithesin (3 ml/kg ip) and maintained with supplemental doses (0.5 ml/kg ip) administered approximately every 40 minutes up to a period of 13-24 hrs. A heating pad was used to regulate body temperature over the duration of the experiment. The animal was placed in a head holder which left the ears unobstructed in preparation for subsequent insertion of acoustic couplers. Following a midline incision, the inferior colliculus was exposed by removal of the posterior skull and aspiration of the overlying cortex.

Details of Stimulus and Recording Techniques.

Continuous sinusoids from a Hewlett Packard function generator (HP 3310 A) were shaped by a Coulbourn Instruments gate (S84-04) to form tone bursts of 110 ms duration including 10 ms rise and decay times. The shaped signal was split and led through 2 independent passive decade attenuators and a low output impedance power amplifier. In studies of cells tuned to very low tone frequencies (less than about 750 Hz), rise/decay times were extended to as much as 50 ms to eliminate gating transients. Stimulus repetition rate was 1/s.

The signals were transduced by Pioneer SE-50D stereo headphone drivers mounted in shielded housings. The earphone housing opened into a small acoustic coupler whose speculum was inserted into the opening of the rat'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 were obtained at the end of each experiment in dB SPL (sound pressure level re 20 uPa) separately for left and right ears using a Bruel & Kjaer 1/2 inch microphone (type 4134) and probe tube assembly. Stimulus amplitudes were set in dB attenuation during the experiment, and were converted to dB SPL off-line. In situ measurements of acoustical crosstalk between the two ears revealed a value of 65 dB SPL up to 1.5 kHz, and at least 70 dB for all higher frequencies

The rat was situated in an electrically shielded, sound attenuated room. Insulated tungsten microelectrodes (1.3-1.8 MegaOhm at 1 kHz) were used to record the responses of single neurons or small clusters of neurons. Electrical potentials amplified 10,000X by a BAK amplifier (model MDA-4), were displayed on an oscilloscope and fed through an audio amplifier for acoustical monitoring of neural activity. Single neurons were selected for quantitative study with a time amplitude window discriminator (Bak Electronics model DIS-1), and analog delay unit (Bak Electronics model AD-6). Waveforms were displayed on a

Hewlett-Packard oscilloscope (model 120B) and acceptance pulses were led to a Tracor Northern signal averager (TN-1550) for accumulating post-stimulus time histograms.

Experimental Procedures

All electrophysiological responses were recorded from the left IC. Data are reported for 3 rats which received lesions of the ipsilateral SOC, 3 rats with contralateral SOC lesions and 3 rats with bilateral SOC lesions.

For each electrode penetration, the characteristic frequency (CF) was determined for single neurons by examination of the stimulus-synchronized spike record on an oscilloscope and by listening to the amplifier output fed into a loudspeaker. The CF was subsequently used in the determination of monaural and binaural response properties.

Binaural response magnitudes were studied by simultaneously delivering to each ear, contralaterally assessed best frequency tones. The contralateral intensity level was initially fixed at or near threshold as ipsilateral intensity was incremented in 5 or 10 dB steps from 0 dB SPL. The intensity of the contralateral tone was then set at successively higher levels and the ipsilateral intensity varied in the same manner. This procedure allowed for a wide range of stimulus intensities and interaural intensity differences (IIDs) to be tested.

Binaural responses were subdivided on the basis of the

classification scheme proposed by Goldberg and Brown (1969) and extended by Aitkin et al.(1975). This scheme uses a 3-letter code to designate binaural influences. The first two letters indicate the responses to monaural stimulation of the contralateral and ipsilateral ears (usually excitatory, "E", or no response, "O"). The third letter, separated by a slash mark, indicates the binaural interaction type which is inferred from comparison of monaural and binaural conditions. (facilitation, "F"; inhibition, "I"; mixed facilitation and inhibition, "Mixed"; or no difference "O"). Summation (EE/F) and suppression (EO/I) classes refer to a binaural response which was stronger or weaker, respectively, than responses to one ear alone. The mixed interaction class displayed both summation and suppression responses depending upon the ipsilateral sound pressure level. Ipsilateral stimulation inhibited contralateral responses at high sound pressures, but facilitated responses at lower sound pressures. The facilitatory response was most apparent when the contralateral stimulus was near threshold. Neurons which were responsive to monaural stimulation only (EO/O) were assigned to a separate category (Monaural).

- Interaction interaural intensity differences (interaction IIDs) were assessed by comparing near-threshold contralateral intensity with the lowest ipsilateral intensity which unequivocally produced a summation or suppression response. Interaction IIDs were determined for all cells examined.

At the end of each experiment, the animal was deeply

anesthetized with Equithesin and perfused with saline followed by 10% formalin. The brain was immersed in 10% formalin and later sectioned to examine the extent of the SOC lesions.

Histology

All tissue was sectioned at 40 microns in the frontal plane and subjected to an identical cresyl violet staining procedure for cell bodies. Drawings of standard frontal sections through the SOC of a normal rat were constructed at 200 micron intervals. Brain sections from each lesion case were selected to correspond with the normal standard. In cases with unilateral SOC lesions the number of cells remaining in each of the SOC nuclei on the damaged side were compared with the number of cells in the corresponding nuclei on the contralateral side. In bilateral lesion cases the number of cells which remained in the SOC nuclei were compared with the number of cells in the corresponding nuclei of the standard brain sections. The extent of cell loss within individual nuclei of the SOC was expressed as either complete (95-100%), severe (75-95%), moderate (45-75%) or mild (15-45%). Tissue in which the cell loss was less than 15% was considered normal. The extent of damage in each case was illustrated on the standard sections through a normal rat brain.

RESULTS

Kainic Acid Damage

The photomicrographs of figure 1 show the SOC of an animal (R136) which received a complete unilateral lesion of the right SOC. Plates B and D are low and high power photomicrographs respectively of the SOC ipsilateral to the lesion site. These photomicrographs show the damage to the SOC which resulted from a microinjection of kainic acid into this nucleus. The individual nuclei of the SOC appear shrunken and neurons have been replaced with microglia. Plates A and C show the contralateral SOC under low and high power respectively. The size and shape of the SOC nuclei appear normal under low magnification and individual neurons appear healthy under high magnification. The kainic acid damage of this case is representative of the degeneration encountered in other animals with complete unilateral lesions of the SOC.

Anatomy

Ipsilateral Lesion Cases.

In figure 2 the anatomical reconstructions for rats 118, 129 and 134 are presented. These animals received lesions of the SOC ipsilateral to the recording site. In two of these cases (R118 and R129) the MSO, LSO and LTB were completely degenerated throughout the caudal to rostral extent of the SOC. In the third case, (R134),

Figure 1. Photomicrographs showing the appearance of the superior olivary complex (SOC) in R136 following a unilateral kainic acid lesion of the right SOC. The SOC appeared normal on the left (plate A), but was completely destroyed on the right (plate B). Plates C and D show corresponding high power photomicrographs through the central portion of lateral superior olive (LSO). Note that neurons appear healthy on the left (plate C) but only microglia are present on the right (plate D).

A **B**

500 MICRONS

C **D**

100 MICRONS

Figure 2. Extent of damage in rats with unilateral lesions of the ipsilateral (left) superior olivary complex (SOC). Damage is illustrated at 200 micron intervals on drawings of standard frontal sections through the SOC of a normal rat. Black shading, cross-hatching, parallel lines, and light stipple denote complete, severe, moderate and mild degeneration respectively. Numbers under each drawing indicate distance in millimeters rostral to the anterior extent of the facial nerve nucleus. Abbreviations: MSO, medial superior olive; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; LTB, lateral nucleus of the trapezoid body; SPO, superior paraolivary nucleus; VTB, ventral nucleus of the trapezoid body; TZ, transitional zone; VNLL, ventral nucleus of the lateral lemniscus; VII, facial nerve nucleus.

R118 IPSILATERAL SOC LESION

R129 IPSILATERAL SOC LESION

Figure 2. (continued)

R134 IPSILATERAL SOC LESION

Figure 2. (continued)

cell loss in the LSO, MSO and LTB was complete throughout all but the most rostral extent of the nuclei. In the case of R118, all the nuclei of the SOC ipsilateral to the lesion have degenerated. In addition, the facial nerve nucleus and VNLL were severely damaged. In R129 damage was most extensive at the caudal extreme of the SOC. The MNTB and SPO were completely destroyed caudally while the VTB received severe damage. At the rostral extreme of the SOC, the MNTB was severely degenerated and the SPO received moderate damage while the VTB appeared normal. The facial nerve nucleus and VNLL received only mild damage at the rostral and caudal extent of these nuclei respectively. Damage to the SOC nuclei of R134 was also most extensive at the caudal extreme of the SOC. The MNTB and VTB were severely damaged caudally while the SPO had completely degenerated. At the rostral extent of the SOC, the MNTB and the SPO received moderate damage while the VTB appeared normal. The facial nerve nucleus received mild damage at the rostral extent of the nucleus while the VNLL appeared normal.

Contralateral Lesion Cases.

The extent of damage to the SOC in 3 animals (R119, R126 and R136) which received lesions of the contralateral SOC is shown in figure 3. In each of these cases, the LSO, MSO and LTB were completely destroyed throughout the caudal to rostral extent of the SOC. In the case of R119, all nuclei of the SOC and VNLL were

completely degenerated. In addition, the rostral extreme of the facial nerve nucleus received moderate damage. In R126 most damage occurred at the caudal extreme of the SOC where the MNTB and SPO were completely destroyed and VTB received moderate damage. At the rostral extent of the SOC, the MNTB was severely damaged, the SPO received moderate damage and VTB appeared normal. The facial nerve nucleus appeared normal and VNLL received mild damage only at the caudal extreme of the nucleus. All SOC nuclei of R136 were completely destroyed. The facial nerve nucleus received severe damage, while the VNLL received moderate damage only at the caudal extreme of the nucleus.

Bilateral Lesion Cases.

Three animals (R127, R130 and R133) received bilateral lesions of the SOC (see figure 4). In all cases the LSO and LTB were completely destroyed on both sides. The MSO nuclei were completely destroyed throughout the caudal to rostral extent of the nuclei in R127 and R133. The MSO nuclei of R130 were completely destroyed on both sides throughout all but the most rostral extent of the nuclei.

In the case of R127, the MNTB on the left sustained complete damage at the caudal extreme progressing toward moderate damage at the most rostral extent of the nucleus. The MNTB appeared normal on the right side. The SPO sustained complete damage on the left and moderate damage on the right. The VTB received moderate

Figure 3. Extent of damage in rats with lesions of the contralateral (right) superior olivary complex (SOC). For explanation of symbols and abbreviations see figure 2.

R119 CONTRALATERAL SOC LESION

R126 CONTRALATERAL SOC LESION

Figure 3. (continued)

R136

CONTRALATERAL SOC LESION

Figure 3. (continued)

damage throughout most of the nucleus on the left and was normal on the right except for mild damage at the caudal extent of the nucleus. The facial nerve nucleus received moderate damage on the left and mild damage on the right. The VNLL was normal throughout most of the nucleus on the left and received moderate to mild damage on the right.

In R130 MNTB on the left and the right received moderate damage at the caudal extent of the nucleus yet appeared normal in the most rostral sections. The SPO received moderate damage caudally and mild damage further rostrally on the left and was severely damaged throughout the nucleus on the right. The VTB received moderate damage at the caudal extreme of the nucleus on the left and right yet appeared normal throughout most of the remainder of the nucleus. The rostral extent of the facial nerve nucleus appeared normal on the left and was severely damaged on the right. The VNLL appeared normal on the left and right except for mild damage at the caudal extent of the nucleus on both sides.

In the case of R133, the MNTB was completely destroyed on the left and throughout much of the nucleus on the right. The SPO was severely damaged on the left and received complete damage caudally and severe damage rostrally on the right. The VTB received severe damage on the left and moderate damage on the right. Both facial nerve nuclei received complete damage at the rostral extent of the nuclei. The VNLL on the left and right received moderate damage throughout most of the nucleus.

Figure 4. Extent of damage in rats with bilateral lesions of the superior olivary complex (SOC). For explanation of symbols and abbreviations see figure 2.

R127 BILATERAL SOC LESIONS

CONTINUED OVER

Figure 4. (continued)

R130 BILATERAL SOC LESIONS

Figure 4. (continued)

CONTINUED OVER

Figure 4. (continued)

R133 BILATERAL SOC LESIONS

Figure 4. (continued)

CONTINUED OVER

Figure 4. (continued)

Physiology Monaural Response Characteristics.

Quantitative data are presented for 382 single neurons recorded from the ICC of the 9 animals for which anatomical reconstructions were presented. The tonotopic organization of the ICC was preserved in all SOC lesion cases. Best frequencies progressed from low to high in a dorsolateral to ventromedial orientation. In addition, the units in the ICC of all rats with SOC lesions appeared to be narrowly tuned to sound frequency in accordance with observations of the normal rat ICC (Kelly, Glenn and Beaver). Best frequency thresholds of ipsilateral and bilateral SOC lesion cases appeared to be similar to those found in the IC of normal rats. Best frequency thresholds for normal rats as well as rats with ipsilateral, contralateral and bilateral SOC lesions are shown in figure 5 together with a previously published behavioural audiogram (indicated by solid line) obtained by the conditioned suppression method (Kelly and Masterton, 1977). A correspondence was evident between the lowest physiological thresholds at a given CF and the behavioural absolute threshold at the same frequency. It was also noted that the CF thresholds in each of these cases varied widely at any given frequency. Best frequency thresholds in rats with contralateral SOC lesions appeared to be elevated.

Binaural Interaction

The activity of the neurons in response to binaural stimulation was classified as summation (EE/F), suppression (EO/I), Monaural

Figure 5. Thresholds for eliciting contralateral responses at characteristic frequency for normal rats (Kelly, Glenn and Beaver, in preparation) and rats with ipsilateral, contralateral and bilateral lesions of the superior olivary complex. Dot, threshold data for single electrode penetration. Solid line, average behavioural audiogram obtained by Kelly and Masterton (1977) for the albino rat.

BEST FREQUENCY THRESHOLDS

(EO/O) or Mixed. Neurons whose response patterns were not characteristic of other binaural classes were assigned to a separate category (Other). This classification is in accordance with that used by Kelly, Glenn, and Beaver in examination of the normal rat ICC. The distribution of cell types for the normal rat ICC based on examination of 212 single neurons was 53.6% EO/I, 21.6% EE/F, 20.6% EO/O and 4.5% Other. In the present study percentages based on examination of 122 single neurons in 3 animals with ipsilateral lesions of the SOC were 53.3% EO/I, 26.2 % EE/F 18.9% EO/O and 1.6% Mixed. Percentages based on examination of 129 units in cases with contralateral SOC lesions were 69.7% EO/I, 19.4% EE/F and 10.9% EO/O. The distribution of cell types for animals with bilateral SOC lesions was 66.4% EO/I, 19.9% EE/F and 12.2% EO/O and 1.5% Mixed based on examination of 131 units. A single chi square test of independence performed on the percentages of the major interaction types, EE/F, EO/I and EO/O, indicated no difference between groups. ($\chi^2 (6) = 9.61$, n.s.). A Histogram showing best frequency distributions of normal (Kelly, Glenn and Beaver, in preparation) and SOC lesion animals is presented in figure 6. Data in this figure were grouped within octave band intervals for CFs between 0.5 and 64 kHz. A chi square test of independence indicated that there was no difference between the CF distributions for the normal, ipsilateral, contralateral and bilateral SOC lesion cases ($\chi^2 (18) = 26.7$, n.s.). In all cases the majority (65-79%) of the units had CFs in the frequency range between 4 and 32 kHz. In all rats with SOC lesions

Figure 6 Histogram showing the distribution of characteristic frequencies (CFs) for normal, ipsilateral, contralateral and bilateral SOC lesion rats. Data are grouped within octave band intervals for CFs from 0.5 to 64 kHz. Note that the highest CFs in the octave between 32 and 64 kHz were around 40 kHz. Data obtained from normals (Kelly, Glenn and Beaver, in preparation) is shown as light, ipsilaterals as diagonal lines, contralaterals as horizontal lines and bilaterals as dark.

the major response types (EO/I, EE/F and EO/O) were broadly represented over octave intervals from 1 to 40 kHz with a tendency for suppression responses to be more numerous at higher frequencies (see figure 7). These observations are in accordance with those obtained in the IC of the normal rat (Kelly, Glenn and Beaver, in preparation).

IID Distributions.

Figure 8 presents the distribution of interaction IIDs, which are the smallest interaural intensity difference required to produce a just noticeable binaural interaction (expressed here as ipsilateral minus contralateral dB). These distributions are presented for normal animals (Kelly, Beaver and Glenn, in preparation) as well as those with lesions of the SOC. The histograms of figure 8 illustrate the percentage distribution of interaction IIDs for the binaural summation and suppression classes. Chi square tests of independence were performed on these distributions over the range of IIDs from -10 to +25 dB in order to avoid small expected frequencies.

Binaural Suppression Class. The IID distributions for the binaural suppression class are indicated on the left side of figure 8 by crosshatching. The IID distribution for normal animals was determined for 118 single neurons in the binaural suppression class. Interaction IIDs ranged from -35 to +45 dB with the modal value between +5 dB and +10 dB. The IID distributions for the ipsilateral

Figure 7. Histograms showing the distribution of binaural response types as a function of characteristic frequency (CF) for rats with ipsilateral, contralateral and bilateral lesions of the superior olivary complex. Data are grouped within octave band intervals for CFs between 0.5 and 64 kHz. Note that the highest CFs in the octave between 32 and 64 kHz were around 40 kHz. suppression responses are shown as dark, summation responses as light, and monaural responses as shaded bars.

Figure 8. Histograms showing the percentage distribution of interaction interaural intensity differences (IIDs) for the binaural summation and suppression classes. These distributions are presented for normal rats (Kelly, Glenn and Beaver, in preparation) as well as those with ipsilateral (left), contralateral (right) and bilateral superior olivary complex (SOC) lesions. Positive values of interaction IID indicate an ipsilateral intensity greater than the contralateral intensity. Unshaded bars, interaction IIDs for summation responses. Shaded bars, IIDs for the suppression responses.

SUPPRESSION **SUMMATION**

and contralateral SOC lesion cases were based upon examination of 67 and 90 units respectively. IIDs varied over a range of -15 to +50 dB for the ipsilateral lesion cases and -15 to +30 dB for the contralateral lesion cases. The modal values for each of these cases were between +5 and +10 dB. The IID distribution for the bilateral lesion cases was determined for 88 neurons. The modal IID value for this distribution was between +20 and +25 dB and IIDs ranged from -10 to +55 dB. IID distributions for the ipsilateral and contralateral groups did not differ significantly from those obtained for normal rats. (ipsilateral vs. normal $\chi^2 (6) = 4.34$, n.s.; contralateral vs. normal $\chi^2 (6) = 2.92$, n.s.). However, the distribution of interaction IID for the bilateral cases differed significantly from normal distribution ($\chi^2 (6) = 41.81$, $p < .05$)

Binaural Summation Class. IID distributions for the binaural summation class are indicated in the second half of figure 8. The IID distribution for normal animals was determined for 48 neurons in the binaural summation class. The IID distribution varied over a range of -15 to +45 dB with the modal value between +5 and +10 dB. The IID distribution for the ipsilateral SOC lesion cases was based upon examination of 33 neurons. Interaction IIDs varied over a range of -10 to +45 dB with a modal value between 0 and +5 dB. IIDs for the contralateral SOC lesion cases were determined for 25 neurons. This distribution had a range of -25 to +35dB and a modal value between +5 and +10 dB. The interaction IID distribution for the bilateral SOC lesion cases was based upon examination of 26

neurons. The interaction IIDs ranged from -10 to +40 dB with a modal value between +15 and +20 dB. There was no significant difference between the IID distributions obtained for the unilateral SOC lesion animals and normal cases (ipsilateral vs. normal $X^2 (6) = 5.60$, n.s.; contralateral vs. normal $X^2 (6) = 11.18$, n.s.). The IID distribution for bilateral SOC lesion animals, however, differed significantly from the normal distribution ($X^2 (6) = 26.5$, $p < .05$).

IID Distributions For Bilateral SOC Lesion Rats. The individual IID distributions for unilateral SOC lesion animals did not markedly differ from the composite distributions and will not therefore be presented. Individual IID distributions will be presented for each of the bilateral SOC lesion cases, however, since the composite IID distribution differed from the normal distribution. Individual IID distributions for the bilateral SOC lesion cases (R127, R130 and R133) are presented in figure 9. The modal IID values for the binaural suppression class were between +20 and +25 dB for R127, between +15 to +20 for R130 and between +10 to +15 for R133. It is noteworthy that modal IID values for all bilateral animals were greater than those obtained for normal rats. The modal IID values for the binaural summation class were between +10 to +15 dB for R127, between +10 and +20 dB for R130 and between +15 to +20 dB for R133. Again, modal IID values for all rats with bilateral SOC lesions were greater than those found in the normal rat ICC.

Figure 9. Histograms showing the distribution of interaction interaural intensity differences (IIDs) for individual animals with bilateral superior olivary complex (SOC) lesions. Positive values of interaction IID indicate ipsilateral intensity greater than contralateral intensity. Unshaded bars, interaction IIDs for summation responses. Shaded bars, interaction IIDs for suppression responses.

BILATERAL SOC LESIONS**SUPPRESSION****SUMMATION**

Latency Distributions.

The mean minimum latent period for neurons in the IC of the normal rat is 7.86 msec (n=21). Latencies ranged from 5 to 14 msec (Kelly, Beaver and Glenn, in preparation). Histograms showing the percentage distributions of minimum latencies for animals with complete lesions of the SOC are presented in figure 10. Data are presented for an animal with an ipsilateral SOC lesion (R129), contralateral SOC lesion (R136) and 3 rats with bilateral SOC lesions (R127, R130 and R133)². A composite distribution is presented for bilateral SOC lesion cases. The mean latency for the ipsilateral SOC lesion case, R129, was 8.00 msec (n=44). The mean latency for the case with a contralateral SOC lesion, R136, was 8.33 msec (n=50). The mean latencies for each of the bilateral SOC lesion rats were as follows: 10.28 msec (n=37) for R127, 9.80 msec (n=45) for R130 and 10.47 msec (n=36) for R133. An analysis of variance indicated that the mean latencies differed significantly ($F(5, 227) = 12.16, p < .05$). Student Newman-Keul's posthoc comparisons indicated a significant difference between each of the bilateral cases and the normal case ($p < .05$). The bilaterals did not, however, differ from each other. The range of latency values appeared similar for normal and SOC lesion rats. An analysis of

² Minimum latencies were not systematically investigated in the first 4 animals of this study. The importance of this parameter became evident upon examination of latencies in the first bilateral SOC lesion animal. It is for this reason that only one ipsilateral and one contralateral SOC lesion case are presented.

Figure 10. Histograms showing the percentage distributions of minimum latencies for rats with complete lesions of the SOC. Distributions are presented for a rat with an ipsilateral (left) superior olivary complex (SOC) lesion (R129) and contralateral (right) SOC lesion (R136). A composite distribution is presented for the three bilateral SOC lesion cases (R127, R130 and R133).

variance indicated that minimum latencies did not vary as a function of cell type (summation, suppression or monaural) for any of the SOC lesion cases (ipsilateral $F(2, 39) = 2.04$, n.s.; contralateral $F(2, 47) = .7712$, n.s. ; bilateral $F(2, 114) = 1.56$, n.s.).

DISCUSSION

Monaural Response Properties

The results of the present study indicated that ipsilateral and bilateral SOC lesions had no effect upon monaural response characteristics in terms of best frequency representation, tonotopic organization and sharpness of tuning of IC neurons. Lesions of the contralateral SOC, however, appeared to produce an elevation in best frequency thresholds although other monaural response properties examined in these animals appeared normal. It seems remarkable that lesions of the contralateral SOC produce elevated thresholds whereas bilateral SOC lesions do not. Lesions of the right (contralateral) SOC in bilateral SOC lesion rats were not, however, as extensive as the lesions in the contralateral SOC lesion group. Thus, it is possible that the extent of the contralateral lesion may be related the observed threshold elevation. An examination of best frequency thresholds for individual animals has revealed that thresholds for the bilateral SOC lesion animal with the largest contralateral lesion, R133, did appear to be somewhat elevated. This further supports the hypothesis of a relation between contralateral lesion size and threshold. This question requires further study.

Mean minimum latencies to contralateral stimulation obtained from unilateral SOC lesion animals did not differ from normal animals. However, mean latencies obtained from bilateral SOC

lesion animals were significantly longer than those in the normal rat IC (Kelly, Glenn and Beaver, in preparation). Increased latencies may result from longer pathways, synaptic delays or slower conduction rates. It is not possible at this time to suggest a most probable mechanism for the observed differences in minimum latencies.

Binaural Interaction

The major binaural response types of summation and suppression were found in the IC of animals with both unilateral and bilateral lesions of the SOC. The proportions of these response types in the IC of all SOC lesion animals were similar to those found in normal rat IC (Kelly, Beaver and Glenn, in preparation).

Bilateral Lesion Cases

Bilateral SOC lesions produced a significant change in IID sensitivity. Binaural interaction in these cases tended to occur when the ipsilateral intensity was 10 to 25 dB greater than the contralateral intensity. In contrast, in normal rats binaural interaction often occurred when the ipsilateral intensity was close to, or only slightly greater than the contralateral intensity (Kelly, Glenn and Beaver, in preparation).

Common to all bilateral lesion cases was the loss of the LSO, MSO and LTB on both sides. Thus, one or more of these nuclei must be important for maintaining normal interactions. Indeed,

electrophysiological, anatomical and behavioral evidence suggest that the MSO and LSO are specialized for processing small differences in interaural time and intensity. Anatomical studies have shown that there is a convergence of input from the two ears in each of these nuclei (Glendenning et al., 1985; Goldberg and Brown, 1968, Harrison and Irvine, 1966; Harrison and Warr, 1962; Stotler, 1953) and electrophysiological studies have shown that the majority of units within the MSO and LSO are binaurally sensitive (Boudreau and Tsuchitani, 1968; Caird and Klinke, 1983; Galambos et al., 1959; Goldberg and Brown, 1968, 1969; Guinan et al., 1972a,b; Hall, 1965; Harnischfeger et al., 1985; Inbody and Feng, 1981; Tsuchitani, 1977; Tsuchitani and Boudreau, 1969). In addition, a recent behavioural study (Kavanagh and Kelly, in preparation) has demonstrated that kainic acid lesions of these nuclei in ferrets severely disrupt the ability to localize sound in space. Thus, the elevation of IIDs in bilateral SOC lesion animals may have been due to the fact that the LSO and MSO were not present.

Perhaps more surprising, given the extent of damage present in the bilateral lesion cases, is the fact that the IIDs were merely elevated and not totally abolished. The origin of these interactions must be examined. This study provides evidence that binaural integration must occur above the level of the SOC. A bilateral SOC lesion case, R133, was presented in which all the nuclei of the SOC were completely destroyed on both sides. In this animal binaural integration must have occurred within higher auditory structures.

There are several possible nuclei above the level of the SOC in which binaural integration may take place. Binaural integration may take place within the VNLL, DNLL or the IC itself. The VNLL receives direct input from each cochlear nucleus and projects to the IC.

Although the major source of ascending afferents to the VNLL arise from the contralateral VCN (cat: Glendenning et al., 1981; van Noort, 1969; Warr, 1966, 1969, 1972), a small dorsomedial region of the VNLL in both cat (Glendenning et al., 1981; Warr, 1966) and rhesus monkey (Strominger and Strominger, 1971) is unique in that receives a dense projection almost exclusively from the ipsilateral VCN.

Thus, binaural innervation of some of the neurons is possible.

Moreover, since the VNLL projects to the ipsilateral IC (cat: Adams, 1979; Brunso-Bechtold et al., 1981; Elverland, 1978; Goldberg and Moore, 1967; Kudo, 1981; van Noort, 1969; Roth et al 1978; Whitley and Henkel, 1984; rat: Beyerl, 1978; Coleman and Clerici, 1987; opossum: Willard and Martin, 1983; and mouse: Willard and Ryugo, 1983) it may be considered a possible source of binaural interaction.

Although binaurally sensitive cells have been found in the VNLL (Aitkin et al., 1970; Guinan et al., 1972a,b), these interactions may arise from ipsilateral afferents from the SOC (cat: Elverland, 1978; Glendenning et al., 1981) rather than direct input from the cochlear nuclei. The presence of binaurally sensitive cells in the VNLL is therefore a necessary, but not sufficient condition to establish this nucleus as a source of binaural integration.

The DNLL and IC do not receive direct input from both cochlear

nuclei, however, binaural integration may originate within these nuclei through commissural connections. The commissure of the lateral lemniscus (CLL) originates from the DNLL and terminates in the DNLL and IC of the opposite side (Glendenning et al., 1981). This commissure allows an opportunity for convergence of input from both ears upon a cell in the DNLL or IC. The DNLL has strong projections to ipsilateral IC and also projects to the contralateral DNLL and IC via CLL (cat: Adams, 1979; Brunso-Bechtold et al., 1981; Elverland, 1978; Goldberg and Moore, 1967; Kudo, 1981; van Noort, 1969; Roth et al 1978; Whitley and Henkel, 1984; rat: Beyerl, 1978; Coleman and Clerici, 1987; opossum: Willard and Martin, 1983; and mouse: Willard and Ryugo, 1983). Thus, the commissure of the lateral lemniscus provides an opportunity for binaural integration in the DNLL or IC.

Binaural integration may also originate within the IC via a second commissure, the commissure of the inferior colliculus. The commissure of the inferior colliculus provides an opportunity for binaural interaction by connecting homologous regions of the inferior colliculus on the two sides. Intercollicular connections have been described in the rat (Druga and Syka, Beyerl, 1978; Coleman and Clerici, 1978) bat (Schweitzer, 1981; Zook and Casseday, 1982) monkey (Barnes et al., 1943), rabbit (Tarlov and Moore, 1966) and cat (Moore and Goldberg, 1963; and Rockel and Jones, 1973). It is thus possible that binaural processing may also occur at the level of the IC through commissural connections. The

significance of commissural pathways to binaural processing is not known at this time.

Given the above discussion, it is clear that there are several nuclei above the level of the SOC in which binaural processing may take place. However the following question remains. Why do many interaction IIDs appear to be elevated in bilateral SOC lesion cases? One possible explanation is that extra-olivary cells are not equally responsive to ipsilateral and contralateral stimulation. Contralateral stimulation may more effectively influence the discharge rate of such a neuron. It may be suggested that an increased number or efficiency of contralateral as opposed to ipsilateral input may establish contralateral dominance. In order for ipsilateral stimulation to be as effective as contralateral stimulation the intensity at the ipsilateral ear would have to be substantially greater than that at the contralateral ear. These neurons may not exhibit binaural interaction unless the ipsilateral intensity markedly exceeds the contralateral intensity. Elevated interaction IIDs would consequently result.

An alternative hypothesis suggests that elevated IIDs in bilateral SOC lesion cases may result from a lack of coincidence in the time at which input from each ear reaches binaurally sensitive cells. Pollak (1988) has investigated time-intensity trading in the IC of the bat and has demonstrated that the chief factor determining whether an EI cell discharges is the timing or latency of the inputs. In this study he demonstrated that the response of a cell is

suppressed when the inhibitory component arrives at the same time or earlier than the excitatory component. If the excitatory component arrives at the cell before the inhibitory component, suppression of the response will not occur. Thus the discharge probability of each binaural neuron is determined largely by arrival times of discharges from the excitatory and inhibitory ear.

The hypothesis that sensitivity for intensity disparities may be mediated by a mechanism operating on the temporal coincidence of input from the two ears was first proposed by Jeffress (1948) and has received support from single unit studies in the MSO (Moushegian, 1964; Hall, 1965; Caird and Klinke, 1983) LSO (Caird and Klinke, 1983; superior colliculus (Yin et al., 1985) and auditory cortex (Brugge et al., 1969; Kitzes et al., 1980) of the cat. A longer latency of input from the ipsilateral than contralateral ear would result in a lack of temporal coincidence. However, latency decreases monotonically with increases in signal intensity (Aitkin et al., 1970; Hind et al., 1963). Thus, making the sound louder at the ipsilateral ear should effectively create a shortening in the latency of the inputs arriving from that ear thereby restoring temporal coincidence. Perhaps binaural interaction tends to occur at elevated IIDs in rats with bilateral SOC lesions because of a longer latency of ipsilateral than contralateral input to some of the cells in the IC.

The above theory requires that ipsilateral latencies to monaural stimulation be longer than contralateral latencies. In order to test this hypothesis, latencies to ipsilateral and

contralateral stimulation should be obtained at the threshold of the neuron. The results of the present study indicated that minimum latencies to contralateral stimulation were significantly longer in rats with bilateral SOC lesions than normal rats (Kelly, Glenn and Beaver, in preparation). If the above hypothesis is correct, then latencies to ipsilateral stimulation must be markedly longer than those in the normal rat IC. Further experimentation is required to resolve this issue.

It is important to consider whether the observed changes in the IID sensitivity of cells in bilateral SOC lesion animals would result in an inability of these animals to localize sounds in space. In the rat the binaural intensity cue associated with a sound source located at 90 degrees azimuth is 20 dB at 20 kHz but drops to 6 dB at 4 kHz. The binaural intensity cue is negligible for frequencies below 4 kHz (Harrison and Downey, 1970). Since IIDs are present within this range in bilateral SOC lesion animals it is possible that these rats may be able to localize sounds. This question must be tested experimentally.

Unilateral Lesion Cases

The lack of any apparent abnormality in the binaural interaction patterns of unilateral lesion animals will now be discussed. Unilateral SOC lesions produced no change in the distribution of interaction IIDs. In normal (Kelly, Glenn and Beaver, in preparation) and unilateral SOC lesion rats binaural interaction

often occurred when the ipsilateral intensity was close to, or slightly greater than the contralateral intensity.

In almost all unilateral lesion animals LSO and MSO were completely destroyed. These nuclei have been extensively investigated in terms of binaural processing. The LSO and MSO gain afferents from both ears - a critical prerequisite for binaural processing. The MSO is characterized by both binaural summation and suppression responses, whereas cells in the LSO are almost exclusively excited by ipsilateral stimulation and inhibited by contralateral stimulation (Boudreau and Tsuchitani, 1968; Guinan et al., 1972a,b). There is some indication that cells in the LSO have predominately high-frequency CF's, whereas the MSO is dominated by low-frequency responses (Brugge and Geisler, 1978; Masterton and Imig, 1984). Degeneration and tracer studies across a broad range of mammalian species including the rat have indicated that the MSO projects to the ipsilateral IC, while the LSO projects bilaterally to the IC (cat: Adams, 1979; Brunso-Bechtold et al., 1981; Roth et al., 1978; Stotler, 1953; rat: Beyerl, 1978; Coleman and Clerici, 1987; opossum: Willard and Martin, 1983; kangaroo rat: Browner and Webster, 1975 and bat: Zook and Casseday, 1982). It appears that the excitatory projection of the LSO to the IC may be strictly contralateral. The ipsilateral projection of the LSO to the IC is believed to be inhibitory on the basis of the following evidence. There is an absence of IE cells in the IC, these would be expected on the basis of the ipsilateral projection of the LSO. In addition, a

recent pharmacological study (Saint-Marie et al., 1989) has suggested that the inhibitory transmitter glycine may be used by the uncrossed input of the LSO to the IC.

On the basis of the projections of the LSO and MSO to the IC it may be expected that a unilateral lesion of the SOC would result in an absence of summation responses in the IC ipsilateral to the lesion. Moreover, it would be reasonable to predict an absence of high frequency suppression responses in the IC contralateral to the lesion. These predictions are not, in fact, borne out. A likely explanation for this unexpected finding is that both of these nuclei also project to an intermediary nucleus, the dorsal nucleus of the lateral lemniscus (DNLL). The MSO projects to the ipsilateral DNLL, while the LSO sends bilateral projections to this nucleus (Glendenning and Masterton, 1981). The DNLL in turn sends bilateral projections to the IC (Adams, 1979; Bruno-Bechtold et al., 1981; Elverland, 1978; Goldberg and Moore, 1967; van Noort, 1969; Roth et al., 1978; Whitley and Henkel, 1984). The afferents of the LSO and MSO to this nucleus may be responsible for the normal complement of binaural interaction types in unilateral SOC lesion animals.

It is also possible that the binaural interactions in unilateral SOC lesion animals originate within other nuclei of the SOC. Little is known about the binaural responses of smaller nuclei within the olivary complex (Guinan et al., 1972a,b). However, two of these nuclei (VTB and LTB) meet the criteria which distinguish them as possible sources of binaural integration. These nuclei receive input

from each ear, project to the IC and contain binaurally sensitive cells.

The major projection to the VTB is from the contralateral VCN (cat: Glendenning et al., 1983; van Noort, 1969; Warr, 1972; rabbit: Borg 1973; dog: Goldberg and Brown, 1968). A weaker ipsilateral input to the VTB has also been indicated (cat: Fernandez and Karapas, 1967; Glendenning and Masterton, 1985; dog: Goldberg and Brown, 1968). The VTB projects to the ipsilateral IC (cat: Adams, 1979; Brunso-Bechtold et al., 1981; Roth et al., 1978; gerbil: Nordeen et al., 1983; bat: Zook and Casseday, 1982; rat: Coleman and Clerici, 1987; Beyerl, 1978; Druga and Syka, 1984; opossum: Willard and Martin, 1983; mouse: Willard and Ryugo, 1983). Although the majority of the cells in this nucleus are monaural, 35-50% of the cells in this nucleus are binaurally sensitive (cat: Goldberg et al., 1963; Guinan et al., 1972 a,b; dog: Goldberg and Brown, 1968).

In a number of species including the rat, the LTB receives a major ascending projection from the ipsilateral VCN (cat: van Noort, 1969; Powell and Cowan, 1962; Stotler, 1953; Warr, 1966, 1972; rabbit: Borg, 1973; dog: Goldberg and Brown, 1968; rat: Harrison and Irvine, 1966). The caudal part of the LTB is also innervated from contralateral dorsal cochlear nucleus (DCN) according to Fernandez and Karapas (1967). Tracer studies in a number of species have indicated that the LTB has bilateral projections to the IC (cat: Adams, 1979; 1983b; Brunso-Bechtold et al., 1981; Roth et al., 1978; gerbil: Nordeen et al., 1983; bat: Zook and Casseday, 1982; rat:

Coleman and Clerici, 1987; Beyerl, 1978; Druga and Syka, 1984; opossum: Willard and Martin, 1983; mouse: Willard and Ryugo, 1983). Although monaural responses are in the majority, binaural summation and suppression units are present within this nucleus (cat: Boudreau and Tsuchitani, 1968; Goldberg et al., 1963; Guinan et al., 1972 a,b; Tsuchitani, 1977). Thus, at least some of the cells in the VTB and LTB receive bilateral input and project to the IC.

Although relatively little is known of the superior paraolivary nucleus (SPO), this nucleus send afferents to the ipsilateral IC in the rat (Beyerl, 1978; Coleman and Clerici, 1987; Druga and Syka, 1984) mouse (Willard and Ryugo, 1983) and opossum (Willard and Martin, 1983) and therefore must be considered a possible source of binaural integration. Although afferents to this nucleus have not been fully delineated, anterograde degeneration studies in the mouse and opossum have indicated a strong projection to this nucleus from the dorsal cochlear nucleus (Willard and Martin, 1983). Binaural interaction in the SPO has not been described.

Other possible sources of binaural integration in unilateral SOC lesion animals are nuclei above the level of the SOC. However, the finding that modal IID values for unilateral lesion rats differed from all bilateral lesion animals suggests that at least some of the interactions originated from nuclei within the contralateral SOC.

It is important to consider whether the rats with unilateral lesions of the SOC would be capable of localizing sounds in space. Kavanagh and Kelly (in preparation) have recently demonstrated that

ferrets with unilateral SOC lesions in fact show severe impairments in sound localization. The authors suggest that accurate localization may depend upon the combined activity of both SOC. The cells responsive to auditory stimulation in unilateral SOC lesion animals may receive input predominately from the remaining olive. Thus, the IID sensitivity of the cells in the IC of unilateral lesion animals may not predict the ability of these animals to localize sounds in space

Conclusions

This study has been the first to show that binaural interactions remain in the IC following complete bilateral lesions of the SOC and consequently, has been the first to demonstrate that binaural integration occurs above the level of the SOC. In addition, evidence is provided that nuclei of the SOC, namely the LSO and MSO, are essential for maintaining a normal pattern of binaural interaction. Future studies may resolve the relative contribution of individual nuclei of the SOC and higher auditory structures to binaural processing in the auditory system.

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APPENDIX

List of Abbreviations

CF	characteristic frequency
CLL	commissure of the lateral lemniscus
DCN	dorsal cochlear nucleus
DNLL	dorsal nucleus of the lateral lemniscus
EE (EE/F)	binaural response type-cell excited by stimulation of either ear alone
EI (EO/I)	binaural response type-cell excited by contralateral stimulation and inhibited by ipsilateral stimulation.
EO (EO/O)	binaural response type-cell excited by contralateral stimulation, ipsilateral stimulation has no effect.
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
LSO	lateral superior olivary nucleus
LTB	lateral nucleus of the trapezoid body

MNTB	medial nucleus of the trapezoid body
MSO	medial superior olivary nucleus
SOC	superior olivary complex
SPO	superior paraolivary nucleus
VCN	ventral division of the cochlear nucleus
VNLL	ventral nucleus of the lateral lemniscus
VTB	ventral nucleus of the trapezoid body

END

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