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**Physiological Response Properties of Neurons in the Dorsal Cortex of the Inferior
Colliculus**

By

Jean-Christian Maillet

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

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Abstract

The present study examined the physiological response properties of neurons in the dorsal cortex of the inferior colliculus (ICD). To date only a few studies have examined response characteristics of ICD neurons to sound stimulation. In vivo single-unit recordings of ICD neurons were performed on male adult Wistar albino rats (*Rattus norvegicus*; 300-450g). Of the 33 neurons in the sample, 10 neurons displayed habituation while 23 neurons did not display habituation. For neurons not showing habituation, 8 responded to tone bursts and noise bursts and 15 neurons responded to noise bursts and not to tone bursts. Among the most interesting findings of the present study were the 4 noise neurons that responded with an “on-off” firing pattern. Such a response pattern suggests that ICD neurons may contribute to the processing of duration of complex sounds, such as those found in the natural environment.

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Dedicated to the Memory of Sheldon Carroll

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List of Abbreviations

AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AVCN	Anteroventral Cochlear Nucleus
CoIC	Commissure of the Inferior Colliculus
CF	Characteristic Frequency
CNQX	6-cyano-7-nitroquinoxaline-2,3-dione
DCN	Dorsal Cochlear Nucleus
DNLL	Dorsal Nucleus of the Lateral Lemniscus
DNQX	6, 7-Dinitroquinoxaline-2, 3-dione
EPSP	Excitatory Post-Synaptic Potential
FTC	Frequency Tuning Curves
GABA	γ -amino butyric acid
IC	Inferior Colliculus
ICC	Central Nucleus of the Inferior Colliculus
ICD	Dorsal Cortex of the Inferior Colliculus
ICX	External Cortex of the Inferior Colliculus
ILD	Interaural Level Difference
INLL	Intermediate Nucleus of the Lateral Lemniscus
IPSP	Inhibitory Post-Synaptic Potential
LSO	Lateral Superior Olive
MGN	Medial Geniculate Nucleus
MSO	Medial Superior Olive
MT	Minimum Threshold

NBQX	1, 2, 3, 4-tetrahydro-6-nitro-2, 3-dioxo-benzo[f] quinoxaline-7-sulfonamide disodium
NMDA	N-Methyl-D-aspartate
PHA-L	Phaseolus vulgaris-leucoagglutinin
PSTH	Peri-stimulus time histogram
RLF	Rate/Level Function
VNLL	Ventral Nucleus of the Lateral Lemniscus

Introduction

The inferior colliculus (IC) is a key structure in the central auditory system. This auditory nucleus can be subdivided on the basis of cellular morphology and neural projection pattern. Each subdivision in the IC is thought to play different roles in the processing of auditory information. Although the terminology used to subdivide the IC varies greatly, a common anatomical pattern is easily identified. The terminology used in the present study will be based on that used by Faye-Lund and Osen (1985), which recognizes a central nucleus (ICC), an external cortex (ICX) and a dorsal cortex (ICD).

The contribution of the ICC to the processing of auditory information was under extensive investigation in the last several decades. Therefore, much knowledge has been obtained about the function of this auditory structure. In contrast, less is known about the functional contributions of the cortical subdivisions of IC, especially the ICD. This project was therefore designed to examine the physiological response characteristics of neurons in the ICD. Because the ICD receives innervation from other subdivisions of the IC and these innervations may in turn affect neural responses in the ICD, it is important to have an overall understanding of the anatomy and physiology of the ICD as well as the ICC and ICX.

Anatomy of the Subdivisions of the Inferior Colliculus

Central Nucleus of the Inferior Colliculus

The ICC is composed primarily of disc-shaped and stellate cells (Morest & Oliver, 1984; Oliver & Morest, 1984). Disc-Shaped cells have dendritic fields ranging from approximately 200 to 800 μm in diameter and are arranged in sheet-like fashion. These cells are distinguished on the basis of the size of the soma and dendritic field and

are categorized as being either large, large-medium, or small. Stellate cells are characterized by a spherical-shaped dendritic field. Stellate cells can also be distinguished on the basis of the shape and size of soma and dendritic field. Stellate cells can be further categorized as being either simple or complex and as being small, medium or large.

The soma and dendrites of disc-shaped cells appear to be oriented parallel to one another in a dorsomedial to ventrolateral axis along a rostrocaudal plane forming fibrodendritic laminae (Faye-Lund & Osen, 1985; Morest & Oliver, 1984; Oliver & Morest, 1984). The fibrodendritic laminae are one of the most visually striking features of the ICC, and it appears to also provide an anatomical basis for tonotopic organization (see page 9) in the ICC (Oliver & Shneiderman, 1991).

Stellate cells appear to lack orientation; however their dendritic fields appear to cross several fibrodendritic laminae in a mediolateral direction (Faye-Lund & Osen, 1985; Morest & Oliver, 1984; Oliver & Morest, 1984). The dendritic fields of stellate cells that cross several fibrodendritic laminae may provide an anatomical basis for the convergence of inputs that are associated with different frequencies onto a single inferior collicular neuron, thus refining auditory processing (Oliver & Shneiderman, 1991).

External Cortex of the Inferior Colliculus

The ICX wraps around the ICC laterally and rostrally. It is distinguished from the ICC in three ways: (1) the exclusive presence of stellate cells, (2) a lesser packing density of cells and (3) the absence of fibrodendritic laminae (Faye-Lund & Osen, 1985; Morest & Oliver, 1984).

Using the Nissil-staining method, Faye-Lund and Osen (1985) subdivided the ICX into three layers. Layer I is the most superficial layer, containing small neurons about 7 to 9 μm in diameter. Layer II is the most distinct of the three layers, and is located in the lateral and rostral part of the ICX. Cells in layer II appear to be stellate, with thin curved dendrites that are highly interwoven. Layer III, also referred to as the deep part of the ICX, contains stellate cells of small, medium and larger diameter (4-28 μm). The most characteristic element of layer III is large stellate neurons with coarse Nissil-stained bodies, which are not found anywhere else in the IC.

The Dorsal Cortex

The ICD is located dorsomedial to the ICC. The ICD contains predominantly stellate cells without obvious dendritic orientation, and as is the case with the ICX, the ICD lacks fibrodendritic laminae (Faye-Lund & Osen, 1985; Morest & Oliver, 1984). Morest and Oliver (1984) recognized four distinct layers of the ICD. Layer I contains small and medium-sized neurons with flattened dendritic fields that parallel the surface of the IC. Layer II is filled with small to medium stellate cells that appear to intermingle with layer I, forming an area often referred to as the pericentral region. Layer III contains stellate cells that vary from small to large with various branching patterns with various numbers of dendritic spines. At rostral levels the medial part of layer III adjoins with the commissure of the inferior colliculus (CoIC). Finally, layer IV is filled with stellate cells of all sizes and forms a lens-shape structure, which borders the ICC with an axis parallel to that of the fibrodendritic laminae.

Neural Projections to the Inferior Colliculus

Ascending Projections

Virtually all lower auditory nuclei send ascending projections to the IC, with the majority of these projections synapsing in the ICC (Oliver & Shneiderman, 1991). It appears that the IC is not simply a relay nucleus, but rather a site where monaural and binaural information from lower auditory nuclei is integrated.

Electron microscopic autoradiographs and retrograde tract tracing experiments revealed that some monaural projections to the ICC stemmed from the anteroventral cochlear nucleus (AVCN), the posteroventral cochlear nucleus (PVCN) and the dorsal cochlear nucleus (DCN) (Brunso-Bechtold et al., 1981; Oliver, 1985). The PVCN and AVCN inputs are most dense in the ventral part of the ICC, while the inputs from the DCN appear to be most dense in the dorsal part of the ICC. Another important monaural projection to the ICC stems from the ventral nucleus of the lateral lemniscus (VNLL). Both retrograde and anterograde tracing studies reveal that the neurons in the VNLL send most or all of its projections to the ICC and this projection is stronger to the rostral and ventrolateral portions of the ICC (Brunso-Bechtold et al., 1981; Covey & Casseday, 1986; Kudo, 1981; Malmeierca et al., 1998; Merchan & Berbel, 1996; Whitely & Henkel, 1984; Zook & Casseday, 1982).

Injections of horseradish peroxidase (HRP) into the ICC of cats have revealed that the binaural inputs to this structure are from the lateral superior olive (LSO) and medial superior olive (MSO) (Adams, 1979; Brunso-Bechtold et al., 1981). This pattern of innervation has also been observed in a variety of other mammals (Beyerl, 1978; Druga & Syka, 1984; Nordeen et al., 1983; Willard & Martin, 1983, 1984; Zook & Casseday,

& Syka, 1984; Nordeen et al., 1983; Willard & Martin, 1983, 1984; Zook & Casseday, 1982). Researchers have also found that the ICC receives ascending binaural inputs from the dorsal nucleus of the lateral lemniscus (DNLL) (Adams, 1979; Brunso-Bechtold et al., 1981; Li & Kelly, 1992; Merchan et al., 1994; Oliver & Shneiderman, 1989; Shneiderman & Oliver, 1989; Shneiderman et al., 1988).

Although the majority of the ascending projections to the IC terminate in the central nucleus, a small number of ascending projections appear to terminate in the cortical IC (ICX and ICD). Coleman and Clerici (1987) injected the retrograde tracer HRP in the ICX and found labeled neurons in the ipsilateral DNLL and contralateral DCN and PVCN. Studies using retrograde tracer also established that the ipsilateral DNLL and the contralateral DCN project to layer IV of the ICD, while the contralateral AVCN project to both layer III and IV of the ICD. These ascending projections to the cortical IC appear to be predominantly monaural in nature (Oliver & Shneiderman, 1991).

Intrinsic and Commissural Projections

Intrinsic projections within the IC allow its three subnuclei to communicate with one another. The commissure of the inferior colliculus (CoIC) allows the subnuclei of the one IC to communicate with the subnuclei of the other IC.

Saldana and Merchan (1992) made iontophoretic injections of Phaseolus vulgaris-leucoagglutinin (PHA-L) into ICC of rats. These injections resulted in the presence of a “main band” and an “external band”. Interestingly, these bands were located in both the IC ipsilateral and contralateral to the injection site, thus confirming the presence of both intrinsic and commissural projections. Another study using the iontophoretic injections

of biocytin in the ICC resulted in similar banded patterns (Malmierca et al., 1995). The main band extends dorsomedially and ventrolaterally from the injection site and runs parallel to the fibrodendritic laminae in such a manner that it spans the entire length of the ICC and extends into the ICD. The external band is located in the ICX and is oriented dorsoventrally. The external band is basically perpendicular to the fibrodendritic laminae in the ICC.

Although the specific roles of the intrinsic and commissural projections are not yet well understood, propositions have been made about the functional significance of these projections in the processing of auditory information. For instance, Malmierca et al. (1995) suggested that the extension of the main band into the ICD might serve as a means to maintain frequency specific relationship between the ICC and ICD. They also suggested that the perpendicular orientation of the external band to the fibrodendritic laminae might provide ICX neurons with converging inputs from different isofrequency laminae, thus providing a possible explanation to the characteristic broad tuning and lack of tonotopicity in the ICX.

Descending Projections

The IC receives descending projections from the superior colliculus, the medial geniculate nucleus (MGN) and the auditory cortex (Huffman & Hanson, 1991). The major source of the descending projections to the IC is from the auditory cortex. This descending projection has therefore received an extensive study. In general, the descending projections from the auditory cortex originate in the pyramidal cell layer V. Retrograde tract tracing studies demonstrate that the descending projections are topographically organized. For instance, area 41 of the auditory cortex projects

bilaterally to the deep layers II and III of the ICD, area 36 projects ipsilaterally to layer I of the ICD, while area 22 of the auditory cortex projects ipsilaterally to layers II and III or the ICX (Coleman & Clerici, 1986).

Saldana et al. (1996) further examined the organization of the corticocollicular projections. Injections of PHA-L in the auditory cortex of the rat revealed the presence of two bands in the IC. The lateral band appeared predominantly in the ICX, while a medial band extended through the ICD into the ICC. Although the functional significance of these bands are not yet well understood, it is interesting to point out that the orientation of these bands mimic the orientation of the intracollicular bands that were present after the injection of PHA-L in the ICC.

Neurotransmitters of the Inferior Colliculus

Both excitatory and inhibitory neurotransmitters were found in the inferior colliculus. Excitation and inhibition regulate auditory responses and are therefore involved in the processing of auditory information in the IC.

The major excitatory neurotransmitter of the IC includes the excitatory amino acid glutamate. Glutamatergic neurotransmission in the IC appear to be mediated by α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and N-Methyl-D-aspartate (NMDA) receptors (Faingold et al., 1989b; Feldman & Knudsen, 1994; Kelly & Zhang, 2002; Ma et al., 2002; Zhang & Kelly, 2001). The sources of the excitatory inputs from the IC are from the contralateral cochlear nucleus (Adams, 1979; Brunso-Bechtold et al., 1981), the contralateral LSO (Glendenning et al., 1992; Saint Marie et al., 1989) and ipsilateral MSO (Adams, 1979; Brunso-Bechtold et al., 1981; Vater et al., 1995).

The major inhibitory neurotransmitters of the IC include γ -amino-butyric acid (GABA) and glycine. The GABAergic inhibition appear to be mediated predominantly by GABA_A receptors whereas glycinergic inhibition appears to be mediated by glycine receptors (Burge & Pollak, 2001; Chen et al., 1999; Faingold et al., 1989a; Fuzessery & Hall, 1996; Li & Kelly, 1992; Koch & Grothe, 1998; Le Beau et al., 1996; Park & Pollak, 1993; Winer et al., 1995; Zhang et al., 1998). The major GABAergic projections to the IC appear to come from the contralateral DNLL via the commissure of Probst (Burger & Pollak, 2001; Chen et al., 1998; Li & Kelly, 1992; Zhang et al., 1998), the ipsilateral VNLL (Gonzalez-Hernandez et al., 1996; Winer et al., 1995; Vater et al., 1997; Zhang et al., 1998) and commissural projections from the CoIC (Moore et al., 1998; Smith, 1992). The major glycinergic inputs to the IC originate from the ipsilateral LSO (Glendenning et al., 1992; Saint Marie & Baker, 1990; Saint Marie et al., 1989) and the ipsilateral INLL and VNLL (Winer et al., 1995; Saint Marie & Baker, 1990; Vater et al., 1997).

Physiological Responses of the Inferior Colliculus to Sound Stimulation

Frequency Tuning

The majority of neurons in the ICC show V-shaped frequency tuning curves (FTC) which are tuned to single frequencies (Aitkin et al., 1975; Merzenich & Reid, 1974; Rose et al., 1963; Clopton & Winfield, 1973). In contrast to the ICC, FTCs of ICD neurons appear to be more broadly tuned (Aitkin, 1986; Aitkin et al., 1975; Merzenich & Reid, 1974; Syka et al., 2000).

Frequency tuning curves in the inferior colliculus are typically shaped by the convergence of excitatory and inhibitory inputs. It appears that GABAergic inhibition regulates the width of the FTCs. Several studies have demonstrated that blocking

GABAergic transmission using the GABA_A receptor antagonist bicuculline resulted in a broadening of the FTCs in the ICC (Faingold et al., 1989; Le Beau et al., 1996; Palombi & Caspary, 1996; Pollak & Parks, 1993; Vater et al., 1992).

Tonotopic Organization

As mentioned before, one of the important anatomical features of the ICC is the fibrodendritic laminae. These laminae are believed to provide an anatomical basis for the tonotopic organization of the inferior colliculus. The tonotopicity was confirmed with dorsal to ventral electrode penetration through the cat ICC, which resulted in progressive increases of characteristic frequencies (CFs) (Aitken et al., 1970, 1975; Merzenich & Reid, 1974; Rose et al., 1963). This dorso-to-ventral tonotopic organization has also been shown to be characteristic of the rat ICC (Clopton & Winfield, 1973; Flammino & Clopton, 1975; Kelly et al., 1991).

Some studies have shown that the ICD displays some tonotopic organization, although it does not appear to be as specific as the tonotopicity displayed in the ICC. Aitken (1986) demonstrated through electrode penetrations in the ICD that there is an irregular descending sequence of CFs. This finding is consistent with the anatomical findings of Malmierca et al., (1995) and Saldana and Merchan (1992) which suggests that the extension of their main bands from the ICC to the ICD may serve as a means of conserving frequency specific information.

Intensity Coding

Intensity coding is typically examined by rate-level functions (RLFs). Aitkin (1991) recognizes 3 different classes of RLFs in the ICC: monotonic, non-monotonic and saturated. For monotonic RLFs, the number of action potentials or spikes increases along

with the intensity of the stimulus. For non-monotonic RLFs the number of spikes increases along with the intensity of the stimulus to a maximal point where any subsequent increase in sound intensity results in a reduction of spikes. Finally, for saturated RLFs the number of spikes increases along with stimulus intensity to a maximal point, where it will remain constant as stimulus intensity increases.

Whereas all auditory nerve fibers show monotonic RLFs (Sachs & Abbas, 1974; Palmer & Evans, 1980), many neurons the IC exhibit non-monotonic RLFs. The non-monotonicity is usually attributed to an interaction between excitatory and inhibitory inputs. Iontophoretic application of bicuculline and strychnine, antagonists specific to GABA_A and glycine receptors, increased the firing rate and selectively blocked the firing reduction at the high intensities, converting non-monotonic RLFs into monotonic ones (Faingold et al., 1989; Fuzessery & Hall, 1996; Le Beau et al., 1996; Palombi & Caspary, 1996). Iontophoretic application of AMPA and NMDA receptor antagonists 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f] quinoxaline-7-sulfonamide disodium (NBQX) and ((±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) on single neurons in the ICC resulted in a reduction in firing rates at every sound pressure level that normally elicited a normal excitatory response (Zhang & Kelly, 2001).

In a recent study by Syka et al (2000), it was shown that there appeared to be more non-monotonic RLFs in the ICC than in the ICD. The authors interpreted this finding as being an indication of stronger inhibition in the ICC than in the ICD.

Binaural Response Properties

The majority of neurons in the ICC are binaurally sensitive. In the rat, studies have reported that excitatory/inhibitory (E/I) interactions were found in the majority of

ICC neurons (Flammino & Clopton, 1975; Kelly et al., 1991; Li & Kelly, 1992; Sally & Kelly; 1992; Silverman & Clopton, 1977).

The binaural properties of E/I neurons are established by the interaction between excitatory and inhibitory inputs. The excitatory inputs are from the cochlear nucleus (Brunso-Bechtold et al., 1981; Oliver, 1985) the contralateral LSO (Glendenning et al., 1992; Saint Marie et al., 1989) and the ipsilateral MSO (Adams, 1979; Brunso-Betchtold et al., 1981). The inhibitory inputs are from the ipsilateral LSO which are thought to be glycinergic (Glendenning et al., 1992; Saint Marie et al., 1989) from the ipsilateral VNLL (Gonzalez-Hernandez et al., 1996; Winer et al., 1995) and the contralateral DNLL via the commissure of Probst, and are GABAergic (Burger & Pollak, 2000; Chen et al., 1999; Gonzalez-Hernandez et al., 1996; Winer et al., 1995; Zhang et al., 1998). As a result of the interplay between the excitatory and inhibitory inputs, most neurons in the ICC are excited by contralateral stimulation but are inhibited by ipsilateral stimulation.

Rationale and Specific Aims of the Present Study

Up to date few studies have been conducted examining the response characteristics of ICC neurons to sound stimulation. The majority of studies focused on the characteristics of ICC neurons whereas the responses of ICD neurons were typically recorded in electrode penetrations en route to the ICC (e.g. Aitken et al., 1975; Merzenich & Reid, 1974). In another study, only monaural response characteristics were examined (Syka et al., 2000). These studies could hardly yield firm conclusions. However, these studies do provide valuable suggestions and speculations for further testing.

The current study intends to examine the response characteristics in the ICD by systematically changing spectral, temporal and dichotic parameters of sounds. With an emphasis on the following characteristics:

Habituation

Habituation has been observed in ICD neurons in some studies (Aitkin et al., 1975; Merzenich et al., 1974) however it has never been systematically evaluated. Neurons with habituation respond to a first train of stimuli and thereafter respond erratically or not at all. Habituation of responses in the ICD neurons may be inheritance from auditory cortex neurons showing habituation (see Clarey et al., 1992 for review). Habituation in ICD neurons may also be created by inhibitory innervation from ascending, intrinsic and commissural projections.

To systematically study habituation in ICD neurons, the interstimulus interval was changed to find whether neurons stopped showing habituation under certain stimulus conditions.

Frequency Selectivity of ICD Neurons

Previous studies indicate that there appears to be a slightly irregular tonotopic organization to the ICD. Furthermore, ICD neurons appear to be more broadly tuned than ICC neurons. In some cases ICD neurons appear to preferentially respond to more complex sounds such as noise bursts. Although these studies provide valuable suggestions for further studying the frequency selectivity of ICD neurons, no firm conclusions can yet be drawn.

Anatomical studies suggest that band within the ICC extend into the ICD, yet it is still unclear whether ICD neurons receive convergence of frequency specific inputs.

Evidence for a convergence of inputs from various isofrequency laminae onto ICD neurons could account for the broadness of frequency tuning curves. In order to study frequency tuning in the ICD, frequency tuning curves (FTCs) were collected and sharpness of the frequency tuning of ICD neurons were determined by calculating the Q_{10} values (see page 18 for the definition of Q_{10})

The Characterization of Temporal Firing Patterns of ICD Neurons

Syka et al. (2000) observed that on average, ICD neurons had longer 1st spike latencies compared to ICC neurons. This particular study is the only one that directly examined the temporal response properties of neurons in the ICD and further study would be needed to confirm and expand upon this finding.

ICD neurons receive their major ascending input from the ICC (Malmierca et al., 1995; Saldana & Merchan, 1992). The extra synapse may result in longer response latencies in ICD neurons compared to those of the ICC.

ICD neurons also receive commissural and cortical innervation. These innervations may also modulate temporal response characteristics of ICD neurons. Smith (1992) showed that the commissural projections were in part inhibitory. These inhibitory projections may contribute to lengthening the response latencies. Other studies have shown that NMDA receptors are involved in mediating excitatory neural responses in the ICC (e.g. Zhang & Kelly, 2001) and ICX (e.g. Feldman & Knudsen, 1994; Jen et al., 2001). Although there is no direct evidence available, it is likely that NMDA receptors are also involved in the mediation of these neural responses in the ICD. The slow activation and voltage dependence of NMDA receptors may result in further change in temporal response characteristics (see Kelly & Zhang, 2002 for review). Both inhibitory

innervation and the presence of NMDA receptors in the ICD may modify temporal response characteristics such as the PSTH.

In the proposed study, 1st spike latencies and shape of PSTHs in the rat ICD was studied. The results were compared with those by Syka et al. (2000).

Binaural Interaction in ICD Neurons

Up until now, only Aitkin et al. (1975) examined the binaural response in the ICD. Based on their results, the majority of their ICD neurons appeared to be monaural. However some neurons were binaural E/I neurons, i.e. they received contralateral excitation and ipsilateral inhibition. One neuron in their sample was an E/E neuron, receiving both ipsilateral and contralateral excitation. It is well known that most ICC neurons in the rat are binaural and as such, these binaural properties may be inherited by ICD neurons.

Commissural inputs might add a further step of binaural processing. Smith (1992) electrically stimulated the CoIC in a brain slice preparation and subsequently recorded an IPSP-EPSP-IPSP response in ICD neurons. This pattern was pharmacologically dissected. The results showed that the GABA_A receptor antagonist bicuculline blocked both IPSPs, whereas the non-NMDA receptor antagonists 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 6,7-Dinitroquinoxaline-2,3-dione (DNQX) blocked the EPSP and partially blocked the second IPSP component. The result therefore indicated that the latter IPSP might be generated by a polysynaptic pathway (Smith, 1992). These results not only support the claim that ICD neurons receive commissural inputs, but also suggest that these inputs may result in modification of interaural-level-difference (ILD) curves when compared to those of ICC neurons.

Interaural-level-difference curves were obtained for ICD neurons in the present study. Attempts were made to determine whether or no there are emerging binaural response characteristics in ICD neurons.

Material and Methods

Animal Preparation

Experiments were conducted on male adult Wistar albino rats (*Rattus norvegicus*; 300-450g) obtained from Charles River Canada, St. Constant, Quebec. The external ears and tympanic membrane of all animals were examined with an otoscope and determined to be free of infection and other abnormalities. Surgical anesthetic was induced with a mixture of xylazine (.5mg/kg i.m.) and ketamine hydrochloride (.6mg/kg i.m.). A state of areflexia was maintained with supplemental injection at about every hour with 1/3 of the original dose of the anesthetics. A midline incision was made in the scalp, the skin and muscles was retracted laterally, and a small craniotomy was made to permit insertion of a glass pipette into the ICD for recording. Small bone screws were placed in the skull and fixed to a stainless steel rod with dental acrylic. The rod was then attached to a stereotaxic frame holding the head firmly in place while leaving the external ear free for insertion of earphone drivers. Recordings were made with the rats inside a single-wall, sound attenuated booth (Eckel Industries).

All procedures were approved by the Carleton University Animal Care Committee and were in accordance with the guidelines of the Canadian Council on Animal Care.

Sounds Stimulation

Sounds were presented monaurally to the left ear or binaurally to both ears through a pair of sealed headphone and coupler sets (Beyerdynamic DT 48). Each coupler was connected to a hollow speculum that was inserted into the rat's external meatus. The acoustic waveforms were generated digitally by MaLab 881 software and controlled by a Macintosh G-3 computer. The sound generating and data acquisition system (MaLab 881) was designed and produced by Steve Kaiser, Department of Neurobiology, University of California, Irvine (Kaiser Instruments).

The sound stimuli used in this study consisted of noise bursts and tone bursts. Noise bursts of 100 ms in duration with a 10 ms rise and fall time were used as a search stimulus to identify an ICD neuron. Once a neuron was isolated, 100 ms tone bursts with a 10 ms rise and fall time was used to determine the response parameters of ICD neurons (parameters described in detail in the experimental protocol subsection).

The sound pressure level for all stimuli was calibrated over a frequency range of 1000-40,000 Hz using a condenser microphone (Bruel and Kjaer 4134) with the headphone assembly fitted into an enclosed chamber constructed from tygon tubing. The acoustic response of the headphone assembly was adjusted on-line to provide a constant sound pressure over the range from 500 Hz to 20 kHz.

Recording

A glass pipette was used to register neural activity from ICD neurons. The tip of the recording electrode was 2-3 μm in diameter. The electrode was filled with 3M potassium chloride. The electrode assembly was driven by a Burleigh 6000 ULN model micropositioner. Neural activity registered by the pipette was amplified by a Dagan EX

4-400 Quad differential amplifiers and monitored audiovisually. Neural responses were digitized and discriminated on the basis of amplitude and waveform using an A/D converter and MaLab 881 software. A window discriminator was used to isolate spikes from background activity. The occurrence time of spikes were recorded with a 1- μ s resolution, stored on the computer and processed later with standard database and graphic software.

Recording Procedure and Experimental Protocol

During a recording session, the right ICD was approached obliquely with the electrode tilted 45° relative to the sagittal plane and pitched backwards at a 45° angle. The stereotaxic coordinates were referenced to a point of 3.2mm lateral and 0.6 to 0.4 mm caudal to lambda. The electrode was then lowered into the brain to a depth between 2.8 to 5 mm while monitoring for responses to acoustic stimulation.

Noise bursts were presented to the left ear to search for responsive neurons. After an auditory neuron was identified, it was determined whether the neuron responded to noise bursts only or both to tone bursts and noise bursts. Response characteristics were evaluated for the two groups of neurons, i.e., those responding both to tone and noise bursts as well as those responding to noise bursts only.

Neurons Responding to Tone Bursts

Neurons Showing Habituation

Degree of Habituation

The degree of habituation was determined by varying the interstimulus interval of the sound stimulus. Typically neurons showing habituation first received 20 repetitions of the stimulation at the rate of 1 burst per second. Then stimuli with repetition rates of 1

sweep per 2, 4, 8 and 16 seconds were then used and the number of spikes was recorded at these repetition rates. The inter-stimulus intervals were used in an alternating sequence i.e. 1, 8, 2, 16, 4 seconds. Habituation curves were obtained to graphically demonstrate the degree of habituation by plotting the number of spikes as a function of inter-stimulus interval.

Neurons not Showing Habituation

Frequency Tuning

From neurons not showing habituation and responding to both tone and noise bursts, the characteristic frequency (CF, the frequency at which a neuron shows the lowest response threshold) was noted. Response thresholds were determined over a wide range of frequencies, therefore the frequency tuning curve (FTC) could be generated. An indication of the sharpness of the frequency tuning curve was evaluated with a Q_{10} value ($Q_{10} = \text{CF}/\text{Bandwidth at 10 dB above CF threshold}$). The narrower the frequency range in which the neuron responds, the higher the Q_{10} value.

Rate-level Function

Rate-level functions were generated at a cell's CF by systematically varying the sound pressure level of the tone burst.

Peri-Stimulus Time Histograms

The type of response displayed by an ICD neuron was evaluated by examining the PSTH for a stimulus at "low", "medium" and "high" intensities. Based on the PSTH, first spike latencies were determined by examining the elapsed time between the onset of the sound stimulation and the appearance of the first spike that could clearly be attributed to sound stimulation.

Interaural-Level Differences (ILD) Curves

To create an ILD curve, dichotic stimulation was generated using a pair of headphones. For neurons that responded to tone bursts, ILD curves were determined at the cell's CF. The intensity of the left speaker (stimulating the contralateral ear) was set at a constant sound pressure level (typically 10-20 dB above the threshold), while the intensity of the right speaker (stimulating the ipsilateral ear) was changed systematically from low sound pressure to high.

Neurons Responding to Noise Bursts

Neurons Showing Habituation

The degree of habituation was determined for neurons that responded to noise bursts and not to tone bursts. Habituation curves for these neurons were also obtained by varying the inter-stimulus interval in the same fashion as tone burst neurons.

Neurons Not Showing Habituation

Rate-level Functions

Rate-level functions were generated by systematically varying the sound pressure of the noise burst.

Peri-Stimulus Time Histograms

The type of response for ICD neurons only responding to noise bursts was evaluated by examining the PSTH in response to noise bursts presented at "low", "medium" and "high" intensities. Based on the PSTH first spike latencies were determined in the same fashion as for tone burst neurons.

Interaural-Level Differences (ILD) Curves

Interaural level differences curves for neurons responding only to noise bursts were generated in the same manner as the ones generated for tone burst neurons. The intensity of the left speaker remained constant at a level approximately 10-20 dB above threshold, while the intensity of the right speaker was changed systematically from low sound pressure to high.

Histological Analysis

In order to confirm the stereotaxic coordinates to the ICD, pressure injections of dye were made following recording session. A glass micropipette (20 μ m at the tip) filled with 3% pontamine sky blue in 3M sodium acetate was lowered into the brain using the stereotaxic coordinates of 3.2 mm lateral and 0.6 to 0.4 mm caudal to lambda and while monitoring for auditory field potentials. When auditory responses were obtained, 1 μ L of pontamine sky blue was injected into the brain by applying pressure.

Immediately after the pressure injection, the rat was given an overdose of sodium pentobarbital (120 mg/kg) and perfused transcardially with 0.9% saline followed by a 4% paraformaldehyde in 100 mM phosphate buffer. The brains were removed, postfixed for 4 hours at 4° C, stored overnight in 30% sucrose and cut serially at 80 μ m in the frontal plane on a freezing microtome. Sections were mounted on gelatinized slides and air dried overnight. Alternate sections were stained with cresyl violet or were mounted unstained and coverslipped with Depex (BDH Chemicals, Poole, England) for observation. The results of the dye injections can be seen in Figure 1.

Results

In total, neural responses to acoustic stimulation of 33 ICD neurons were recorded. Sixteen of the 33 neurons responded to both tone bursts and noise bursts. The other 17 neurons responded only to noise bursts.

Neurons with Responses to Tone Bursts

Of the 16 tone burst neurons, 8 displayed habituation when the stimulus repetition rate was 1 sweep/sec. The other 8 did not display habituation at the same repetition rate.

Neurons Showing Habituation

The neuron in Figure 2 shows habituation. Figure 2A shows responses obtained at a rate of 1 sweep per second. As the inter-stimulus interval increases, the neuron fires more spikes. For this particular neuron, when the inter-stimulus interval is 8 seconds (fourth panel), the neuron appeared to fire more spikes overall.

Figure 3 is a habituation curve from the same neuron shown in Figure 2. This neuron fired 12.3 spikes. At an inter-stimulus interval (ISI) of 8 seconds, it fired an average of 65 spikes. At an ISI of 16 seconds, it fired an average of 64 spikes. This neuron displayed recovery from habituation at an ISI of 1 sweep per 8 seconds.

Seven of 8 neurons in the sample displayed recovery from habituation at an ISI of 1 sweep per 8 seconds. The other neuron did not show recovery from habituation. For neurons displaying recovery from habituation, the ISI for the 50% recovery from habituation were determined. Four neurons showed a 50% recovery at an ISI range of 2-4 seconds, while 1 neuron showed a 50% recovery at an ISI range of 1-2 seconds. Finally 1 neuron had a 50% recovery from habituation at an ISI of less than 1 second.

Neurons not Showing Habituation

Non-habituating neurons were analyzed in terms of their frequency tuning, their firing rate-intensity relationship, binaural properties and peri-stimulus time histogram.

Frequency Tuning

We recorded tuning curves from 8 neurons not showing habituation in response to tone bursts. Six of the 8 neurons in the sample displayed a “V” shaped tuning curve such as the one displayed in Figure 4A (CF = 10.0 kHz & MT = 35 dB SPL). One of the remaining 2 neurons displayed a complex tuning curve (Figure 4B) (CF = 10.0 kHz & MT = 65 dB SPL). The other of the remaining 2 neurons displayed a “W” shaped tuning curve (Figure 4C) (CF = 13.0 kHz & MT = 30 dB SPL). Although the neuron in Figure 4C had two troughs, its characteristic frequency was 13.0 kHz and its minimum threshold.

The characteristic frequencies for the 8 neurons ranged from 6.5 kHz to 15.0 kHz (M = 9.87 kHz). The minimum threshold ranging from 0 to 65 dB SPL (M = 33.13 dB SPL). Q10 values were calculated for the 6 neurons displaying a “V” shaped tuning curve, and the values ranged from 2.92 to 9.23 (M = 4.59).

Firing Rate-Stimulus Intensity Relationship

Rate-level functions (RLFs) at CF were obtained for 8 neurons. Five of the 8 neurons displayed saturated RLFs such as the one shown in Figure 5A. Saturated RLF were characterized by an increase in spike count to a maximal point, where it remained constant as stimulus intensity increases. The range within which a neuron’s response increased with stimulus intensity was referred to as the neuron’s dynamic range. The neuron in Figure 5A showed an excitatory threshold of 15 dB SPL and a saturation point

at 35 dB SPL, as such, this neuron's dynamic range was 20 dB SPL. For the 5 neurons, the dynamic range values ranged from 10 to 50 dB SPL ($M = 26.0$ dB SPL).

One neuron had a monotonic RLF (Figure 5B), showing a continuous increase in spike count with stimulus intensity ranging from 65 dB SPL to 80 dB SPL. Finally, the remaining 2 neurons displayed non-monotonic RLFs, i.e. these neurons showed an increased spike count to a maximal point where any further increase in stimulus intensity resulted in a reduction of action potentials. The neuron in Figure 5C displayed an increase in firing between 15 to 45 dB SPL, followed by a decrease in firing between 45 to 75 dB SPL.

Binaural Properties

Interaural level differences (ILD) curves were plotted for all 8 neurons showing responses to tone bursts. Of the 8 neurons, 4 displayed E/O ILD curves such as the one plotted in Figure 6A, showing responses to contralateral stimulation only. The remaining 4 neurons showed E/I ILD curves i.e. these neurons were excited by contralateral stimulation and inhibited by ipsilateral stimulation, such as the one in Figure 6B. This particular neuron's responses systematically decreased as the interaural level difference increased from -30 to 0 dB.

Peri-Stimulus Time Histograms

Peri-stimulus time histograms (PSTHs) were examined for all 8 neurons showing responses to tone bursts. These neurons displayed either an onset firing pattern (i.e., spikes were shown only at the onset of the stimulus) or a sustained pattern (i.e. spikes were shown through out the duration of the stimulus).

Of the 8 neurons, 5 displayed an onset firing pattern. For three of these onset neurons, the spikes were tightly locked to the onset of the stimulus (Figure 7A). For the remaining 2 neurons there was a strong response at the onset of the stimulus. The response then gradually decreased to 0 before the end of the stimulus (100ms) (Figure 7B).

The remaining 3 neurons displayed a sustained firing pattern. One of these neurons responded with a relatively constant firing rate throughout the duration of the stimulus (Figure 7C). Another neuron displayed a prominent transient component at the onset of the stimulus, and a gradual decrease of firing throughout the entire duration of the stimulus (Figure 7D). The final neuron displayed a pause between the prominent transient component and the rest of the continuous firing (Figure 7E).

First spike latencies for all 8 neurons were measured. The 1st spike latencies ranged from 14.22 to 52.02 ms ($M = 27.22$ ms). Generally, there was an inverse relationship between 1st spike latency and stimulus intensity, i.e. the 1st spike latency decreased as the intensity increased. At 10 dB above threshold, the mean 1st spike latency was 27.22, however at high intensity such as 60-70 dB SPL above threshold, the average 1st spike latency decreased to an average of 18.29 ms.

Neurons with Responses to Noise Bursts

There were 17 neurons showing responses to noise bursts only. Of the 17 neurons, 2 neurons showed habituation and 15 did not show habituation at 1 sweep/second. The habituating neurons were analyzed separately from the non-habituating neurons in the same manner as tone burst neurons.

Neurons Showing Habituation

Habituation curves were plotted for the 2 neurons. One of these 2 neurons displayed a 50% recovery at an ISI between 1-2 seconds and a full recovery at an ISI of 8 seconds (figure 8). The second neuron did not show any recovery from habituation.

Neurons not showing Habituation

Firing Rate-Stimulus Intensity Relationship

Rate-level functions were obtained for the 15 noise response neurons. Five of the 15 neurons displayed saturated RLFs (Figure 9A). The neuron in Figure 9A had an excitatory threshold at 30 dB SPL and a saturation point at 60 dB SPL, yielding a dynamic range of 30 dB SPL. The dynamic range of these 5 neurons ranged from 10 to 40 dB SPL ($M = 30.0$ dB SPL). Three neurons displayed monotonic RLFs. For example, the monotonic neuron in Figure 9B showed a continuous increase in firing from 35 to 70 dB SPL. The remaining three neurons displayed non-monotonic RLF. For example the neuron in Figure 9C showed an increase in firing from 40 to 60 dB SPL, which was subsequently followed by a decrease in firing as the intensity was increased to 70 and 80 dB SPL. Two neurons demonstrated consistent firing rate at all suprathreshold intensities. Finally, 2 neurons displayed complex RLFs that did not fall into any of the above groups.

Binaural Properties

Interaural level differences (ILDs) curves were generated for the 15 neurons. Of the 15 neurons, 6 showed E/O types of ILD curve (Figure 10A). Seven of the binaural neurons were E/I. As shown in Figure 10B, this particular neuron's response systematically decreased as the interaural level difference was increased from -50 to 10

dB. The remaining 2 neurons were E/E neurons, indicating that they are excited by both ipsilateral and contralateral stimulation. For example, in Figure 10C, this neuron displays an increase in firing as the interaural difference increases from -50 to 20 dB. Finally 2 neurons displayed complex RLFs that did not fall into any of the above groups.

Peri-stimulus Time Histograms

Peri-stimulus time histograms (PSTHs) were obtained for all 15 neurons responding to noise only. Of the 15 neurons, 2 showed a response locked to the onset of the stimulus, whereas 8 neurons showed a response that was sustained for the entire duration of the stimulus. Four neurons displayed a response locked to the onset and offset of the stimulus, and one neuron displayed a response only at the offset of the stimulus.

Of the two neurons showing an onset firing pattern, 1 showed a response tightly locked to the onset of the stimulus (Figure 11A). Of the 8 neurons showing a response that was sustained for the duration of the stimulus, 4 neurons responded with a relatively constant firing rate throughout the duration of the stimulus (Figure 11B). Three other neurons displayed a pause between the prominent transient component and the rest of the continuous firing (Figure 11C). Finally, two neurons displayed a prominent component at the onset of the stimulus, and a gradual decrease of firing throughout the entire duration of the stimulus (Figure 11D).

The remaining 4 of the 15 neurons displayed an “on-off” firing pattern. As shown in Figure 12A, the cell responds with an onset component that is tightly locked to the onset of the sound. The neuron then paused throughout the duration of the noise bursts. At the offset of the stimulus, the neuron generated spikes with their latencies tightly

locked. Finally, 1 of the 15 neurons displayed a response only at the offset of the stimulus (Figure 13).

First spike latencies were measured for all 14 neurons showing a response to the onset of the noise burst. The 1st spike latencies ranged from 12.52 to 47.77 ms ($M = 24.86$ ms). The average 1st spike latencies for neurons responding to noise burst appeared to increase slightly with increasing intensity. At 10 dB above threshold the average 1st spike latency was 24.85 ms. At 30-40 dB above threshold the average increased to 27.36 ms and at 40 dB + above threshold, the average latency was 25.86 ms.

Latency of offset response for noise response neurons were calculated on 5 neurons that displayed an offset component. At 10 dB above threshold, the latency of offset response ranged from 4.94 to 26.43 ms ($M = 16.36$ ms). At 30-40 dB above threshold, the latency of offset response ranged from 7.66 to 19.53 ms ($M = 13.73$ ms). At 40 dB+ above threshold, the offset component had latencies ranging from 6.19 to 27.01 ms ($M = 15.84$). Although there was some variability in the average offset latency of neurons for various intensities, no systematic change was found in the length latency of offset response as a function of intensity.

Discussion

The present study investigated physiological response characteristics of ICD neurons. The results showed that ICD neurons responded to tone and noise bursts with distinct characteristics compared with ICC neurons, from which ICD neurons receive major ascending inputs. Approximately half of the ICD neurons in this study responded to noise bursts but not to tone bursts. Approximately one third of ICD neurons displayed habituation to repetitive stimuli. Some neurons with responses only to noise bursts but

not to tone bursts displayed “on-off” firing pattern. These responses were rarely observed in the ICC.

Response characteristics of ICD neurons to acoustic stimulation have been previously reported in cats (Aitkin et al., 1975) and guinea pigs (Syka et al., 2000). This study was the first to examine the response characteristics of ICD neurons in the rat. The approach used in previous studies by Aitkin et al. (1975) and Syka et al. (2000) were “en route” to the ICC. Their approach may therefore have a limitation of recording from a particular area instead of the entire ICD. This study used stereotaxic coordinates specifically targeting the ICD. This approach allowed for the recording of the entire ICD.

In spite of the differences, the major results are in general agreement with the previous studies. For example, the majority of neurons in this study appeared to prefer broadband stimulation and habituated to repetitive, unchanging stimulation.

Functional Implications

Noise Response

The majority of non-habituating neurons in the sample of ICD neurons responded to noise bursts and not to tone bursts. This finding suggests that while some ICD neurons are still be involved in the processing of frequency specific auditory information, the majority of ICD neurons may play a role in the processing of broadband sounds such as those found in the real-world environment.

Many ICD neurons showed an offset response to noise bursts and 4 neurons displayed an “on-off” response. On-off neurons displayed spikes locked to the onset and the offset of the stimulus. The offset responses observed in this study are similar to those

observed in the bat (Casseday & Covey, 1994; Casseday et al., 2002; Covey & Casseday, 1999; Ehrlich et al., 1997).

Using tone bursts as stimulation, Covey and Casseday (1999) found that some neurons responded with an offset or on-off response. These neurons show a “bandpass” characteristics when they are tested with tone bursts of different durations. When antagonists to GABA and Glycine are applied to duration selective neurons, most lose their bandpass tuning to duration. Therefore Covey and Casseday suggest that these neurons are specialized for processing of duration information.

On-off neurons in this study may also contribute to the processing of stimulus duration. Specifically, because these on-off neurons only responded to noise bursts but not to tone bursts, they may be particularly important for processing the duration of biologically significant sounds, which are predominantly broadband and complex by nature.

Habituation

Although the exact role of habituation is unknown, it is possible that habituation in the ICD plays a role in reducing the redundancy in signal processing. By reducing or eliminating responses to repeatedly occurring acoustic stimulation, neurons may be better able to detect changes in the acoustical environment.

Neural Mechanisms

Although the exact neural mechanisms governing the response characteristics of ICD neurons still remain unclear, our results suggest that these response characteristics may be due in part to the convergence of excitatory and inhibitory inputs from different sources.

Anatomical studies have demonstrated that the ICD receives intrinsic projections from other subnuclei of the IC and commissural projections from the other side of the IC. Injections of biocytin and PHA-L in the ICC of rats have yield bands that extended from the ICC into the ICD, indicating that the ICD does receive projections from the ICC. Furthermore, these bands were present in the ICC and ICD both ipsilateral to the injection site and contralateral to the injection site, indicating that the ICD also receives commissural projections (Malmierca et al., 1995; Saldana & Merchan, 1992).

Further anatomical studies have revealed that the ICD receives descending projections from the auditory cortex (Huffman & Hanson, 1991). Saldana et al. (1996) examined the organization of the corticocollicular projections and found that PHA-L injections in the auditory cortex yielded two bands. The medial band extended through the ICD into the ICC.

Integration of excitatory and inhibitory inputs from intrinsic, commissural and descending sources results in distinct response characteristics displayed by the ICD.

Preference of Response to Noise Bursts

Seventeen of the 33 neurons in this study responded only to noise bursts and not to tone bursts. In contrast, in the ICC, the major source of input to the ICD, neurons showing preference of response to noise bursts are rare.

Noise burst response may be an indication that these neurons receive many converging, subthreshold excitatory inputs with various frequencies. As previously mentioned anatomical studies have shown that injection of PHA-L and biocytin in the ICC yield a lateral band and a medial band. The medial band extends from the ICC into the ICD. The orientation of the medial band is perpendicular to the layers of the ICD

shown by Morest and Oliver (1984). This anatomical feature, in combination with the predominant presence of stellate cells in the ICD may provide an anatomical basis for the integration of inputs with various frequencies onto single ICD neurons, therefore resulting in neurons which preferentially respond to noise bursts.

Binaural Properties

Of the 23 non-habituating neurons in the sample, 13 were binaural neurons. Binaural neurons were found both in the group of neurons showing response to noise bursts only and in the group of neurons showing response both to tone and noise bursts. Four of the 8 tone burst neurons and 9 of the 15 noise burst neurons were binaural. All 4 of the binaural tone bursts neurons were E/I. Of the 9 binaural noise burst neurons, 7 were E/I neurons and 2 were E/E.

In the ICC, the major ascending source of ICD, binaural neurons are predominantly E/I neurons. The E/I type of binaural interaction was established by the interaction between excitatory and inhibitory inputs of lower auditory structures. ICC neurons typically receive excitatory inputs from the cochlear nucleus (Brunso-Bechtold et al., 1981; Oliver 1985), the contralateral LSO (Glendenning et al., 1992; Saint Marie et al., 1989) and the ipsilateral MSO (Adams, 1979; Brunso-Bechtold et al., 1981). The inhibitory inputs to ICC neurons originate from the ipsilateral LSO (Glendenning et al., 1992; Saint Marie et al., 1989), the ipsilateral VNLL (Gonzalez-Hernandez et al., 1996; Winer et al., 1995) and the contralateral DNLL via the commissure of Probst (Burger & Pollak, 2000; Chen et al., 1999; Gonzalez-Hernandez et al., 1996; Winer et al., 1995; Zhang et al., 1998).

It is likely that the binaural properties of ICD neurons may be partly inherited from ICC neurons. It is also possible that binaural properties of ICD neurons may originate from the opposite IC and is imposed on ICD neurons via the CoIC in a similar manner as that the commissure of Probst contributes to the inhibition of ICC neurons. Brain slice preparation demonstrated that electrical stimulation of the CoIC resulted in an IPSP-EPSP-IPSP response pattern in ICD neurons (Moore et al., 1998; Smith, 1992). Pharmacological dissection revealed the GABA_A antagonist bicuculline blocked both IPSPs. Interestingly, application of non-NMDA antagonists not only eliminated the EPSP, but also partially blocked the second IPSP, indicating that the latter IPSP may be involved in a polysynaptic pathway possibly involving an inhibitory inter-neuron (Moore et al., 1998; Smith, 1992).

Although it is unclear exactly how this IPSP-EPSP-IPSP response pattern affects the binaural characteristics of ICD neurons, it is possible contralateral inhibition is imposed on ICD neurons via an inhibitory interneuron. In vivo studies where the contralateral IC is blocked pharmacologically or where the CoIC is stimulated electrically while monitoring the response of a binaural neuron in the ICD would be needed to better determine the origin of the binaural characteristics.

Peri-Stimulus Time Histograms

The most distinctive feature of the PSTHs of ICD neurons was the on-off firing pattern displayed by neurons responding only to noise bursts. As mentioned above, the on-off firing pattern is perhaps a mechanism for duration discrimination for broadband stimulation.

Although the exact neural mechanism for this response pattern in the ICD is unknown, a model has been proposed for a similar response pattern in the IC of bats. In their model, Covey & Casseday (1999) proposed that the offset response in the IC of the bat was mediated by two major components. The first component is a rebound from inhibition. The inhibition is sustained for the duration of the sound. The second component was a subthreshold transient excitatory input which was evoked by the onset of the stimulus but had a relatively long latency. An offset spike is fired only when the transient excitatory component coincides with the rebound from inhibition. If these two components do not coincide with each other, then both responses remain subthreshold.

The contribution of inhibition to the offset response and the duration tuning was studied by iontophoretic application of bicuculline and strychnine, the GABAA and glycine antagonists. Applications of these antagonists eliminated duration tuning of neurons. Casseday et al. (2002) favored the proposition that this excitation is due to intrinsic membrane properties, especially since neurons in the IC exhibit rebound from inhibition (Peruzzi et al., 2000; Sivaramakrishnan & Oliver, 2001).

It appears that this model for duration tuning in bats is optimal for stimuli of short duration typically < 30 ms. In the present study, the noise bursts were 100 ms in duration. To use the model developed by Covey and Casseday without modification would require a transient excitation with a latency longer than 100 ms. An excitatory input with such a long latency seems unlikely. We propose that a sustained excitation that lasts for the entire duration of the noise bursts, summated with rebound from inhibition results in the offset response. The sustained excitation can be mediated by an NMDA receptor by virtue of its long duration of action. Studies have shown that NMDA

receptors in the ICC are involved in mediating excitatory neural responses (e.g. Zhang & Kelly, 2001) and ICX (e.g. Feldman & Knudsen, 1994; Jen et al., 2001).

Evidence for the contribution of inhibitory component to the offset response in the ICD stem from brain slice studies. Smith (1992) demonstrated that ICD neurons responded with a Ca^{2+} mediated rebound in response to prolonged hyperpolarization. Although the rebound was subthreshold, boost from an NMDA-mediated prolonged excitation would make it suprathreshold. Therefore it would be possible for ICD neurons to produce the offset response. More studies are needed to confirm this hypothesis.

1st Spike Latencies

In general, all 1st spike latencies for the 23 neurons appeared to be longer than those reported for ICC neurons. The longer 1st spike latencies for ICD neurons could be partly because of the extra synapse. Given the large difference in the 1st spike latency between ICC and ICD neurons, we propose that the descending influences from the auditory cortex and local synaptic inhibition may also contribute to the lengthening of 1st spike latencies.

Habituation

Although the exact neural mechanisms governing habituation are unknown, we propose the following possibilities. The first possibility is that habituation in ICD neurons are inherited from the auditory cortex neurons. It has been well established that cortical neurons show habituation (see Clarey et al., 1992 for review), from which the ICD receives many descending projections.

A second possibility is that habituation in the ICD may originate from inhibitory innervations originating from both intrinsic and commissural projections. In such an

instance, inhibition would be responsible for suppressing auditory responses occurring after the first few sweeps of the stimulus.

Finally, it is possible that the reduction in the response was because of reduction in the capability of synaptic receptors to follow repetitive inputs. In this current study, habituation was only evaluated by increasing the inter-stimulus interval. To rule out the possibility that the habituation observed in the present study was because of fatigue, a more rigorous method to evaluate habituation in neurons would be needed in future studies. Such a method could involve changing the stimulus quality such as altering the frequency of the stimulus as well as increasing the inter-stimulus interval.

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Figures

Figure 1. Location of dye injections in the ICD. Stereotaxic coordinates used for the dye injections: 3.2 mm lateral and 0.6 to 0.4 mm caudal to lambda. The 3 dots represent the most common sites of dye in the ICD.

Figure 2. Raster dot histograms for neuron 03c006.000. A. Panels showing the firing of the neuron for the inter-stimuli intervals of 1, 2, 4, 8 and 16 seconds. B. Panels showing the firing of the neuron between 0 and 1 second for each inter-stimuli interval. Dashed lines indicate the onset and offset of the stimulus.

A

B

Figure 3. Habituation curve for neuron 03c006.000. Number of spikes is plotted as a function of ISI. This neuron shows recovery from habituation at an ISI of 1 sweep per 8 seconds. The 50% recovery from habituation is indicated on the graph by a vertical line. The 50% recovery from habituation is at an ISI between 2 and 4 seconds.

Figure 4. Frequency tuning curve (FTC) for ICD neurons. A. Tuning curve for neuron 03c014.000 (CF = 10.0 kHz, MT = 35 dB SPL). B. Tuning curve for neuron 03c010.000 (CF = 10.0 kHz, MT = 65 dB SPL). C. Tuning curve for neuron 03c013.002 (CF = 13.0 kHz, MT = 30 dB).

Figure 5. Rate-level functions (RLFs) for ICD neurons responding to tone bursts. A. Neuron 03c018.001 (CF = 7.0 kHz, MT = 30 dB) displaying a saturated RLF. B. Neuron 03c013.001 (CF = 8.0 kHz, MT = 65 dB) displaying a monotonic RLF. C. Neuron 03c017.004 (CF = 9.5 kHz, MT = 30 dB) displaying a non-monotonic RLF.

A

B

C

Figure 6. Interaural level differences (ILD) curve for ICD neurons responding to tone bursts. A. Neuron 03c013.001 (CF = 8.0 kHz, MT = 65 dB) displaying an E/O ILD curve, contralateral level 80 dB SPL. B. Neuron 03c018.001 (CF = 7.0 kHz, MT = 25 dB) displaying an E/I ILD curve, contralateral level 30 dB SPL.

Figure 7. Peri-stimulus time histograms (PSTHs) for neurons responding to tone bursts. PSTHs based on 20 tone burst sweeps and a bin width of 0.01 seconds. The line below the X axis represents the duration of the tone burst (100 ms). There was a 100 ms delay prior to the onset stimulus. A. Neuron 03c007.002 (CF = 6.5 kHz, MT = 15 dB) showing firing tightly locked with the onset of the stimulus. B. Neuron 03c010.000 (CF = 10.0 kHz, MT = 65 dB) showing strong firing at the onset of the stimulus, which gradually decrease to 0 before the end of the stimulus. C. Neuron 03c017.004 (CF = 9.5 kHz, MT = 30 dB) showing a prominent component at the onset of the stimulus, and a gradual decrease of firing throughout the entire duration of the stimulus.

A

B

C

Figure 8. Habituation curve for neuron 03c012.001. This neuron responded to noise bursts only. Number of spikes is plotted as a function of inter-stimulus interval. This neuron shows recovery from habituation at an ISI of 8 seconds. The 50% recovery from habituation is indicated by a vertical line. The 50% recovery from habituation is at an ISI between 1 and 2 seconds.

Figure 9. Rate-level functions for neurons responding to noise bursts only. A. Neuron 03c.011.002 displaying a saturated RLF. B. Neuron 03c017.003 displaying a monotonic RLF. C. Neuron 03c016.001 displaying a non-monotonic RLF.

A

B

C

Figure 10. Interaural level differences curves for neurons responding to noise bursts only. A. Neuron 03c017.003 displaying an E/O ILD curve, contralateral level 70 dB. B. Neuron 03c011.002 displaying an E/I ILD curve, contralateral level 70 dB. C. Neuron 03c015.003 displaying an E/E ILD curve, contralateral level 50 dB.

A

B

C

Figure 11. Peri-stimulus time histograms (PSTH) for neurons responding to noise bursts only. PSTHs based on 20 noise burst sweeps and a bin width of 10 ms. The line on the X axis represents the duration of the noise burst (100 ms). A. Neuron 03c016 showing firing locked to the onset of the stimulus. B. Neuron 03c015.001 showing relatively constant firing rate throughout the duration of the stimulus. C. Neuron 03c017.000 showing a pause between the prominent transient component and the rest of the continuous firing. D. Neuron 03c018.000 showing a prominent component at the onset of the stimulus, and a gradual decrease of firing throughout the entire duration of the stimulus.

A **B** **C** **D**

Figure 12. Peri-stimulus time histograms (PSTH) for neurons responding to noise bursts only. PSTHs based on 20 noise burst sweeps and a bin width of 10 ms. The line on the X axis represents the duration of the noise burst (100 ms). Neuron 03c011.001 displaying a response only a the offset of the stimulus.

03c011.001

Figure 13. Peri-stimulus time histograms (PSTH) for neurons responding to noise bursts only. PSTHs based on 20 noise burst sweeps and a bin width of 10 ms. The line on the X axis represents the duration of the noise burst (100 ms). Neuron 03c009.000 displays firing only at the onset and offset of the noise burst.

03c009.000

Appendix

Habituation Curves for Neurons Responding to Tone Bursts

Habituation Curves for Neurons Responding to Noise Bursts Only

03c007.002

03c010.002

03c013.001

03c014.000

03c017.004

03c018.001

A

03c007.002

03c010.002

03c014.000

03c018.001

B

03c010.002

03c013.002

03c017.004

C

03c013.001

A

03c007.002

03c010.000

03c010.002

03c013.001

03c017.004

B

03c013.002

03c014.000

03c018.001

A 03c007.002

03c010.000

03c013.001

03c013.002

03c014.000

B 03c010.002

03c017.0004

03c018.001

A

03c009.000

03c011.002

03c016.000

03c016.002

03c017.001

03c018.002

B

03c017.003

03c017.003

C

03c016.001

03c018.000

D

03c011.001

03c015.001

03c015.004

E

03c015.000

03c015.003

A

03c009.000

03c015.000

03c015.004

03c017.000

03c017.001

03c017.003

B

03c011.001

03c011.002

03c015.001

03c016.000

03c016.001

03c018.000

B Con't

03c018.002

C

03c015.003

03c016.002

A**03c015.000** **03c015.001** **03c015.004** **03c016.001** **03c017.001**

A con't

03c017.003

03c018.000

03c018.002

B**03c016.000** **C****03c017.000**

03c009.000

03c011.002

03c016.002

03c015.003

03c011.001