Frequency-Specific Effects on Cochlear Responses During Activation of the Inferior Colliculus in the Guinea Pig

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Submitted 2 December 2003; accepted in final form 25 December 2003

Ota, Y., D. L. Oliver, and D. F. Dolan. Frequency-specific effects on cochlear responses during activation of the inferior colliculus in the guinea pig. J Neurophysiol 91: 2185–2193, 2004. The inferior colliculus (IC) is a major processing center in the ascending auditory pathway. The role of the IC in the descending efferent auditory system is less clear. Although the IC central nucleus (ICC) is the major relay station for the ascending auditory pathways, the IC’s cortex receives its main input from the neocortex and nonauditory sources. The goal of this study was to determine if the IC subdivisions had different functions in the descending efferent auditory system. IC subdivisions were identified by their tuning curves evoked by tone stimulation, and the effects of localized electrical stimulation on the cochlear whole-nerve action potential (CAP). Sharp tuning curves were obtained from ICC in contrast to broad tuning curves from the lateral, external cortex. Electrical stimulation within the central nucleus had a sharply tuned effect on the CAP. The frequency region affected within the cochlea closely matched the best frequency of local cells within the central nucleus. The effect of electrical stimulation within the lateral, external cortex on the CAP was smaller in comparison to central nucleus stimulation. Similar to the broad tuning of cells within the lateral cortex, electrical stimulation had a broad frequency effect on CAP thresholds.

INTRODUCTION

The auditory efferent system begins in the cortex and descends along the general path of the ascending system from the cortex to the inner ear. The inferior colliculus (IC) is a major processing center in the ascending pathway. Descending fibers from the IC project to the superior olivary complex (SOC) and rostral periolivary region to contribute to the efferent system (Caicedo and Herbert 1993; Hoffman and Henson 1990; Malmierca et al. 1996; Shore et al. 1991; Syka et al. 1988a,b). The floor of the fourth ventricle is a converging location for a portion of this descending system and thus a historical location for electrically activating it (Desmedt 1962; Galambos 1956; Wiederhold and Kiang 1970). For reviews of the early literature, see Klinke and Galley (1974), Wiederhold (1986), and Guinan (1996). Due to the compact nature of this fiber bundle, electrical stimulation presumably activates most, if not all, of the medial portion of the crossed olivocochlear (COCB) system that innervates the outer hair cells in the inner ear. Although individual efferent fibers may innervate restricted regions of the cochlea, COCB stimulation causes a fairly broad effect within the cochlea. Electrical activation of individual fibers going to a particular region of the cochlea has not been possible.

More recently, studies have shown that gross electrical activation of the IC produces an efferent effect within the cochlea. Rajan (1988, 1990) first showed a functional efferent connection from the IC to the cochlea by reporting that gross stimulation of the IC reduced the temporary threshold shift of the cochlear whole-nerve action potential (CAP) threshold. Dolan and Nuttall (1988) reported that gross electrical stimulation of the IC via a bipolar electrode reduced the amplitude of the CAP similar to stimulation of COCB at the floor of the fourth ventricle. The physical size of the IC is quite large in comparison to the bundle of COCB fibers at the floor of fourth ventricle, and this allows the placement of microelectrodes to electrically stimulate discrete regions (Mulders and Robertson 2000a; Popelar et al. 2002; Scates et al. 1999).

The architecture and connections of the IC suggest that the parts of the IC may play different roles in the auditory efferent system. The IC is divided into a central nucleus (ICC) surrounded by a dorsal (ICD) and lateral external cortex (ICX) (Faye-Lund 1985; Faye-Lund and Osen 1985; Morest and Oliver 1984). Normal activation of the olivocochlear system may involve the descending projections from the IC to the SOC (Caicedo and Herbert 1993; Mulders and Robertson 2002; Mulders et al. 2003; Schofield and Cant 1999; Thompson and Thompson 1993; Vetter et al. 1993). The ICC sends projections to the periolivary region of the SOC as well as to the dorsal nucleus of the lateral lemniscus and CN (Caicedo and Herbert 1993; Schofield 2001). The ICX also sends descending projections to the periolivary region of the SOC, the CN, and accousticmotor regions (Caicedo and Herbert 1993; Huffman and Henson 1990; Schofield 2001). Unlike the ICC, the ICX and ICD receive neocortical inputs (Huffman and Henson 1990). The ICX receives not only corticocollicular input from auditory and somatosensory neocortex, but it also receives multimodal inputs including inputs from the ICC, dorsal column nuclei, spinal cord, trigeminal nuclei, and superior colliculus (Caicedo and Herbert 1993; Huffman and Henson 1990).

To assess the functional differences of IC subdivisions on cochlear function, the present study used a microelectrode provided by the University of Michigan Center for Neural Communication Technology (Fig. 1) to physiologically characterize the best frequency of IC cells located at the recording
was monitored. Rectal temperature was maintained at 38 °C (1.25 mg/kg im) with supplemental half doses every 2 h.

METHODS

The animal’s head was firmly fixed in a holder while the plastic tip of the speculum was sealed into the left ear canal. The speculum held the dimensions. The electrode tips span a distance of 0.8 mm. Right: enlarged figure; light gray numbers, from 1 to 10, indicate recording sites, while black numbers, from 1 to 5, indicate stimulating sites. The area of each recording and stimulating site is 153 and 1,070 μm², respectively.

electrode position. The same electrode was used to electrically stimulate the same region. The best-frequency region of the electrode position within the IC closely matched the tone burst frequency in which maximum reduction of the CAP was observed. This microstimulation caused varying effects on the CAP depending on which IC subdivision was stimulated.

FIG. 1. The microelectrode used in this study was provided by the University of Michigan Center for Neural Communication Technology. Each electrode has 5 fingers with 2 recording sites and 1 stimulating site per finger. Left: the dimensions. The electrode tips span a distance of 0.8 mm. Right: enlarged figure; light gray numbers, from 1 to 10, indicate recording sites, while black numbers, from 1 to 5, indicate stimulating sites. The area of each recording and stimulating site is 153 and 1,070 μm², respectively.

METH ODS

Pigmented guinea pigs (300–400 g) were anesthetized with ketamine (40 mg/kg im), xylazine (10 mg/kg im) and supplemented with half doses every 1 and 2 h, respectively. One percent lidocaine was administered to the surgical incision points. A tracheotomy was performed, and animals were artificially ventilated while the CO₂ level was monitored. Rectal temperature was maintained at 38 ± 1°C with a heating pad. Paralysis was induced by injection of tubocurarine (1.25 mg/kg im) with supplemental half doses every 2 h.

The animal’s head was firmly fixed in a holder while the plastic tip of the speculum was sealed into the left ear canal. The speculum held a condenser microphone (1/2 in, B&K) to deliver the acoustic tones to evoke the CAP. The microphone was calibrated in a volume approximating the guinea pig external ear canal so that stimulus levels are expressed as dB SPL. CAP threshold to tones (1-ms rise/fall time, 12-ms duration, 10/s, 64 epochs) from 0.5 to 24 kHz were measured at the beginning, during, and at end of the each experiment. Animals were omitted from the data analysis if they showed >10 dB elevations in CAP threshold, compared with normal lab standards, during the experiment or showed elevated CAP thresholds at initial measurement.

The left bulla was exposed and opened to place 0.13-mm diam Teflon-insulated silver wire electrode on the round window. An Ag/AgCl ground electrode was placed in the soft tissue of the neck. The animal was rotated so that an extended right parietal craniotomy was performed to expose the occipital cortex and cerebellum. The occipital cortex was aspirated revealing the dorsal surface of the contralateral IC. The microelectrode (multichannel recording/stimulating electrode provided by The University of Michigan Center for Neural Communication Technology, Fig. 1) was inserted via a micromanipulator into the IC. The electrode has five fingers, and each finger has two recording sites (153 μm²) and a stimulating site (1,070 μm²) to pass current. Spacing of each finger (center to center) is 200 μm. Each stimulating site is positioned equally between the recording sites on each finger. Each recording and stimulating site is numbered as indicated in Fig. 1. The stimulating current was 120–220 μA consisting of biphasic pulses, 250 Hz for 250 ms, and 400 μs of duration for each pulse. Current pulses were passed between adjacent stimulating sites. The tone burst to evoke the CAP was 15 ms after the end of the electrical stimulation. The time between electrical stimulation offset and next electrical stimulation onset was set to 400 ms.

When the probe was inserted into the IC, a tuning curve was obtained from the 10 recording sites with tone bursts (100-ms duration and 400-ms interstimulation interval). The cellular activity of each recording site was audio/visually monitored while varying the frequency and intensity of the tone burst. Note that the cellular activity recorded at each site appeared to be predominately from one cell, but because of the area of the recording site, multiple cells may have contributed to the recording activity. For each frequency, the intensity was noted that produced an increase in spike activity. The tone burst to elicit a CAP was set at 10 dB above threshold [10-dB sensation level (SL)]. Two control responses (64 epochs each) were obtained and averaged. Two responses (64 epochs each) were then obtained with IC stimulation, averaged, and expressed as percent control CAP amplitude. This procedure was repeated for each adjacent pair of stimulating electrodes.

At the end of some experiments, a DC current (30 μA for 5 s or 100 μA for 10 s) was passed through adjacent pairs of stimulating sites to mark the position within the IC. These guinea pigs were given a cardiac perfusion with 4% paraformaldehyde in phosphate buffer. The brain was removed and placed in the preceding solution of JB-4 glycol methacrylate (Polysciences, Warrington, PA) infiltrating solution and 100% ETOH overnight. The brain was then immersed in 100% JB-4 infiltrating solution for 4 ± 24 h. Brains were embedded in plastic molds with JB-4 embedding solution and allowed to polymerize under UV light for 24 h. The resulting blocks were trimmed and 6-μm-thick sections cut on a Leitz 1516 microtome. Every other section through the brain were collected and baked onto a glass slide. Resulting slides were then stained with Paragon and cover slipped with Permount. Each slice was imaged with a light microscope, and the location of the recording and stimulation sites were confirmed.

The experimental protocol was approved by the Animal Care and Use Committee at the University of Michigan and conforms to the National Institutes of Health guidelines for the care and use of laboratory animals.

RESULTS

Sound-driven activity was observed in locations that were confirmed in either the ICC or ICX. All electrode penetrations of the IC were done under visual control, and recordings proceeded immediately as soon as the electrode tip was in the tissue. Responses to tonal stimulation were not evident during the initial part of the penetration, but they were found more deeply. Examples of the locations of recordings and stimulation sites in ICC are shown in a transverse section in Fig. 2. This electrode tip was located near the center of the central nucleus of the IC. A lesion was produced by passing DC current through stimulating sites 3 and 4 of the electrode (Fig. 2, arrow).
The BF of cells located in the ICC in this experiment ranged from ~10 to 16 kHz. Two tuning curves from cells near recording sites 5 and 8 are shown in Fig. 3. The BFs at these sites were 13 and 16 kHz, respectively. Passing current through stimulating sites 3 and 4 produced a localized effect on the CAP with a maximum effect for an acoustic stimulus at 14 kHz. Each tone stimulus used to evoke the CAP was adjusted to be 10 dB above threshold. Increasing the current level increased the reduction in CAP amplitude. CAP amplitude was reduced by ~20–80% for currents from 120 to 220 μA. For each current level, the maximum reduction of the CAP amplitude was largest for the 14-kHz acoustic stimulus.

Similar results from the ICC of a different animal are shown in Figs. 4 and 5. Recordings were obtained from a lateral position in the ICC (Fig. 4) and then repositioned more medially (Fig. 5). The results shown are consistent with seven other animals in which the electrode was placed in a similar location. The recordings from the initial position (Fig. 4) showed tuning curves with cellular BFs ranging from ~4 to 10 kHz (see Fig. 4, top and bottom). Current stimulation through an adjacent stimulating site produced maximum reductions of the CAP amplitude for acoustic stimuli from 5 to 8 kHz (Fig. 4, middle). BFs from cells in the more medial location (Fig. 5, top and bottom) ranged from ~6 to 11.5 kHz. From this more medial position, passing current through adjacent stimulating sites (Fig. 5, middle) affected CAP responses to acoustic stimuli ranging from 6 to 9.5 kHz. The increase in cellular BF with the more medial recording position is consistent with the tonotopic frequency map of the ICC.

The typical effects of electrically stimulating the ICD are shown in Fig. 6. There was no observable affect on CAP amplitude. Similar results were seen in three additional animals in which electrode placements were located at various dorsal locations within the ICD. Electrode placements were confirmed histologically.

Recording and stimulation site in the rostral IC are shown in Fig. 7, A and B. The electrode position included portions of the ICX and the rostral ICC. Two combinations of stimulating sites, 1 and 2 and 4 and 5, were used to pass the DC current to burn the tissue to confirm tip location (Fig. 7, A and B). The lesion located within the ICX was created by stimulating sites 4 and 5. A second lesion (current passed through 1 and 2) was made caudal and medial to the first lesion (Fig. 7B, compare top with bottom) at the transition between the ICC and the rostral pole (RP). Thus this may be considered the most rostral possible recording site in ICC.

The cellular responses from the recording sites within the ICX showed broad tuning without any defined BF (Fig. 8, recording sites 3, 4, and 7–10). Electrical stimulation within the ICX produced broad reduction of the CAP response amplitude (Fig. 8, stimulation sites 4 and 5). In contrast, the responses from the medial site were similar to those from the ICC and showed tuned BFs around 4 kHz (Fig. 8, recording sites 1 and 2). The effect of stimulating sites 1–2, located medial to the ICX, produced a tuned reduction of the CAP matching the recorded response for acoustic stimuli near 4 kHz. This efferent effect matches closely the BF of the cells located near the stimulating sites. These results are similar to three other animals in which the electrode was placed such that it overlapped the ICC and ICX.

Figure 9 shows the range of BFs (● — ●) at a given recording site within the IC and the frequency region within the cochlea maximally affected by current stimulation (○ — ○). There is a close match between BF and tonotopic location within the cochlea. Note that the frequency range of each measure is limited by the number of functioning recording and stimulating sites on the electrode.

**DISCUSSION**

The crossed olivocochlear system has its cells of origin in the vicinity of the SOC (Warr 1975, 1978; Warr and Guinan

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**FIG. 2.** A slice of the inferior colliculus (IC) is shown with a superimposed and appropriately scaled stimulating/recording electrode. The 3 subdivisions of the IC are indicated and provided by the 2nd author. Two visible holes are evident and are a result of passing 100 μA of DC current for 10 s through stimulating sites 3 and 4. Physiological results from this animal are shown in Fig. 3.

**FIG. 3.** The effect of biphasic stimulation at 3 current levels through stimulating sites 3 and 4 on the cochlear whole-nerve action potential (CAP) amplitude (see lower left legend). The reduction of CAP amplitude increased with increasing current level. The peak efferent effect was at 14 kHz and closely matches the best frequencies of the cellular tuning curves recorded at this location (recording sites 5 and 8 gray curves). The affected frequency region within the cochlea was inside the span of best frequencies from cells located at the recording site.
1979; White and Warr 1983) with projections to each cochlea. The efferent system is further divided according to location within the SOC and site of termination within the cochlea. The medial olivocochlear (MOC) system, located in the periolivary nuclei of the SOC (Vetter and Mugnaini 1992; Vetter et al. 1991; White and Warr 1983), innervates the outer hair cells and receives inputs from several locations including the IC (Mulders and Robertson 2000b, 2001; Robertson and Winter 1988; Thompson and Thompson 1991, 1993; Vetter et al. 1993). In addition, in guinea pigs, the MOC fibers give off collaterals to the cochlear nucleus (Benson and Potashner 1990; Winter et al. 1989). Excitatory effects of efferent activation on onset neurons of the cochlear nucleus have been reported (Mulders et al. 2003).

The present results are most likely due to the activation of the MOC and not the middle ear muscles. Scates (Scates et al. 1999) found that the large reductions in DPOAE amplitude from stimulating the IC were unaffected by severing the middle ear muscles in one animal. Their reductions, ≤25 dB, are large compared with the reductions in CAP amplitude equivalent to a 3- to 6-dB reduction in sound pressure reported here. Mulders and Robertson (2000a) investigated IC stimulation with and without paralysis in rats. Large reductions in DPOAE amplitude (5–12 dB) were reduced to 0–3 dB when the rats were paralyzed. The animals in this study were also paralyzed; this should inactivate the middle ear muscles. It is possible that the muscles were not completely paralyzed, but other evidence suggests that the middle ear muscles are not the reason for CAP reduction. Electrical stimulation within the ICD did not produce reduction of the CAP, and this suggests that current spread is not an issue (Mulders and Robertson 2000a). Moreover, the effects we observed were across a range of frequencies, including higher frequencies where middle ear muscle contractions have little effect. Contractions of the middle ear muscles primarily affect low frequency transmission but do not show the high-frequency-specific effects observed here (Borg et al. 1984). Similarly, stimulation of the ICX caused reductions of the CAP that extended to frequencies out of the range of middle ear muscle effects.

IC inputs to the MOC

For the purpose of this physiological study, we simplified the IC structure into three subnuclei. Such simplification allows gross statements about electrical stimulation of the subnuclei, and the effects within the cochlea. The present results showed that activating localized regions of the IC produced differential effects within the cochlea. As in previous studies (Mulders and Robertson 2000a; Scates et al. 1999), stimulation of the dorsal IC (e.g., dorsal cortex) was ineffective, and reductions in cochlear activity occurred only after stimulation...
of the central and lateral regions of the IC. The previously reported reductions in CAP amplitude (Mulders and Robertson 2000a) are also similar to those here.

Some of the previously reported effects of IC stimulation showed frequency preferences but not differences in tuning. For example, the Scates et al. (1999) investigation was limited to relatively low frequencies and reported greater effects at the lowest frequencies used. This may be related to potential middle ear effects or other masking related phenomenon. Mulders and Robertson (2000a) showed a maximal efferent effect for frequencies of 6–10 kHz.

It is possible that the electrical stimulation of the IC produces the effects within the cochlea by some other means than direct input to the MOC neuron. Because the IC is a major processing center for ascending and descending auditory processing, activation of the IC may influence any number of auditory structures. IC stimulation could activate ascending projections and direct cortical inputs to the cochlear nucleus that, in turn, may influence the olivocochlear system (Weedman and Ryugo 1996). We cannot rule out the potential cortical influence in this study, but the simplest pathway for IC activation of MOC neurons is a direct

FIG. 5. In the same animal, the electrode was positioned more medial than in Fig. 4. The characteristic frequencies obtained from recording sites and the frequencies of efferent effect are higher than those of Fig. 4. The BFs ranged from ~6 to 11.5 kHz. The region most affected within the cochlea by passing current at this location in the IC ranged from ~6–9 kHz. Note that the 9th recording site was damaged on repositioning the electrode so no results were obtained from this site.

FIG. 6. Tonal acoustic stimulation produced no driven activity at the recording sites when the electrode was placed within the ICD. Current stimulation had little or no affect on the CAP recorded from the round window of the cochlea.
monosynaptic activation by IC inputs. Other projections from IC directly to the reticular formation are possible and could contribute to MOC activation.

**Fine descending control of the MOC system**

This report shows that the regions of ICC that provide descending input to the periolivary region have sharp tuning. These results are consistent with recent findings on the effects of IC stimulation on olivocochlear function (Mulders and Robertson 2000a; Mulders et al. 2003; Scates et al. 1999) that showed gross electrical stimulation of the IC produced broad efferent effects within the cochlea. However, the individual MOC fibers show sharper tuning characteristics similar to auditory nerve fibers (Brown 1989; Liberman and Brown 1986; Robertson and Gummer 1985). The present findings of sharp tuning in the ICC regions that activate MOC is consistent with an anatomical study (Malmierca et al. 1996) showing a tonotopically organized feedback projection from the ICC to the lower brain stem. Our results suggest that the IC efferent system may exercise a much finer level of influence than the “gross” effects previously described.

Several roles for the medial efferent system have been proposed including a simple attenuator, improving the signal-to-noise ratio, protection from acoustic trauma, and selective attention (Guinan 1996). In general, these proposed roles resulted from studies using electrical stimulation of the COCB at the floor of the fourth ventricle. Such stimulation likely activates most, if not all, of the medial efferent fibers innervating the outer hair cells. In the present study, stimulation of the ICC activates the MOC neurons synaptically rather than electrically. This more physiological stimulation reveals a fine control of the ICC over the MOC in the spectral domain.

The frequency-specific reductions observed with ICC stimulation may provide the basis for the phenomenon of an “attentional filter.” Psychophysical experiments by Scharf and colleagues (Dai et al. 1991; Ebata and Scharf 1992; Scharf 1989; Scharf et al. 1994, 1997) reported a broader “attention filter” in human subjects in which the olivocochlear bundle had been cut by vestibular neurotomy. Because the efferent transection was peripheral to the brain stem, the observed effects can be attributed to elimination of the efferents within the cochlea. These results provide strong evidence that the efferent system can selectively modulate transduction processes within the cochlea.

**Coarse descending control from ICX**

In contrast to ICC, the broad suppression of neural output associated with ICX stimulation may play a role in multimodal selective attention. The ICX is linked with other parts of the auditory system where prominent nonauditory inputs may modulate auditory activity (Malmierca et al. 2002). In this study, we show that ICX can affect cochlear activity via its

![Image](https://via.placeholder.com/150)
The presumed action on the MOC system. The effect of ICX stimulation reduces a broad region of cochlear output, which if desired, would attenuate the auditory sensory input to the CNS in the presence of a nonauditory event. Previous studies suggested that selective attention exists in the auditory system. In the 1970s, Oatman and colleagues (Glenn and Oatman 1977; Oatman 1971, 1976; Oatman and Anderson 1977, 1980) showed that responses recorded from the round window of awake cats were reduced in a visual attention task. More recently, the role of selective attention and arousal state on cochlear emissions has been studied in humans (Ferberf-Viart et al. 1995; Froehlich et al. 1990, 1993a; Michie et al. 1996; Puel et al. 1988). Although Michie et al. (1996) did not find attention related differences in emissions, Froehlich et al. (1993b) found that the arousal state affected the amplitude of the transiently evoked otoacoustic emission (TEOAE). The TEOAE amplitude increases during sleep, and the efferent effect of contralateral noise is reduced during sleep. Thus the ICX control of the olivocochlear systems may differ substantially from that of the ICC.

**GRANTS**

This work was supported by National Institute of Deafness and Other Communication Disorders and Stroke Grants DC-04194, DC-0078, and DC-00189.

**FIG. 8.** The results shown here are from the electrode position shown in Fig. 7. Eight tuning curves were obtained from 8 recording sites. Two of them, located within the ICC, showed narrow tuning curves with low best frequencies. The other 6 response were broadly tuned and from cells in the ICX. Stimulation of the 2 lateral stimulating sites (4 and 5) produced a broad reduction of the CAP. Stimulation of the two medial stimulating sites produced a localized effect in the cochlea with maximum effects at 3 kHz. These frequency specific effects in the cochlea match closely the BFs of cell recorded from sites 1 and 2.

**FIG. 9.** This is a comparison of the range of BFs (● — ●) to the frequency of maximum efferent effect on the CAP (○ — ○) for 11 animals. The low-frequency results (BFs and efferent effect) are typically for recording conditions similar to that shown in Fig. 7. The higher-frequency results (BFs and efferent effects) result from electrode placements more medial in the ICC.
REFERENCES


J Neurophysiol • VOL 91 • MAY 2004 • www.jn.org


