Corticofugal Feedback for Collicular Plasticity Evoked by Electric Stimulation of the Inferior Colliculus

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Zhang, Yongkui and Nobuo Suga. Corticofugal feedback for collicular plasticity evoked by electric stimulation of the inferior colliculus. J Neurophysiol 94: 2676–2682, 2005. First published July 6, 2005; 10.1152/jn.00549.2005. Focal electric stimulation of the auditory cortex, 30-min repetitive acoustic stimulation, and auditory fear conditioning each evoke shifts of the frequency-tuning curves [hereafter, best frequency (BF) shifts] of cortical and collicular neurons. The short-term collicular BF shift is produced by the corticofugal system and primarily depends on the relationship in BF between a recorded collicular and a stimulated cortical neuron or between the BF of a recorded collicular neuron and the frequency of an acoustic stimulus. However, it has been unknown whether focal electric stimulation of the inferior colliculus evokes the collicular BF shift and whether the collicular BF shift, if evoked, depends on corticofugal feedback. In our present research with the awake big brown bat, we found that focal electric stimulation of the cortical BF shifts of collicular neurons located near the stimulated ones; that there were two types of BF shifts: centripetal and centrifugal BF shifts, i.e., shifts toward and shifts away from the BF of stimulated neurons, respectively; and that the development of these collicular BF shifts was blocked by inactivation of the auditory cortex. Our data indicate that the collicular BF shifts (plasticity) evoked by cortical electric stimulation depended on corticofugal feedback. It should be noted that collicular BF shifts also depend on acetylcholine because it has been demonstrated that atropine (an antagonist of muscarinic acetylcholine receptors) applied to the IC blocks the development of collicular BF shifts.

INTRODUCTION

The inferior colliculus (IC) consists of the central nucleus (ICc), external nucleus (ICx), and dorsal nucleus or cortex (ICd). The ICc receives the ascending inputs from several subcortical auditory nuclei (Moorest and Oliver 1984; Oliver and Moorest 1984; Oliver et al. 1991) and projects to the ICx, ICd, the ventral division of the medial geniculate body (MGBv), and the superior colliculus (SC) (Huffman and Hensen 1990; Zhang et al. 1987). The ICc, ICx, and ICd are tonotopically organized (Casseday and Covey 1992; Moorest and Oliver 1984). In the mustached bat and big brown bat, the ICc is well developed, whereas the ICx is not (Casseday and Covey 1992; Zook and Casseday 1987; Zook et al. 1985).

The descending fibers from the primary auditory cortex (AI), i.e., the corticocollicular fibers, terminate in the ICc (Feliciano et al. 1995; Fitzpatrick and Imig 1978; Saldana et al. 1996) as well as in the ICx and ICd (Feliciano and Potashner 1995; Huffman and Hensen 1990). Neurons in the ICx are excited by corticocollicular fibers and in turn inhibit neurons in the ICc (Jen et al. 1998, 2001).

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A long train of repetitive acoustic stimuli comparable to species-specific sounds (Chowdhury and Suga 2000; Gao and Suga 1998; Ma and Suga 2001a; Yan and Suga 1998), focal electric stimulation of the AI (Chowdhury and Suga 2000; Ma and Suga 2001a, 2003), and auditory fear conditioning (Gao and Suga 2000; Ji et al. 2001; Weinberger 1998) each evoke plastic changes in both the AI and ICc. The change in best frequency (BF) is called a BF shift. The collicular BF shift, which is always short term, does not develop when the AI is inactivated during the conditioning (Gao and Suga 1998, 2000). It is evoked by electric stimulation of the AI (Chowdhury and Suga 2000; Ma and Suga 2001a). Therefore the collicular BF shift is evoked by the corticofugal system. Atropine applied to the AI blocks the development of the cortical BF shift elicited by the conditioning but not the collicular BF shift. Therefore the collicular BF shift does not depend on the cortical BF shift but depends on corticofugal feedback (Ji et al. 2001).

As described in the preceding text, the ICc has multiple inputs and outputs in addition to the corticocollicular descending input. It contains many principal cells and interneurons. There is a possibility that the ICc has an intrinsic mechanism for evoking BF shifts without corticofugal feedback. To test this possibility, we electrically stimulated the ICc and found that collicular neurons located near the stimulated ones showed BF shifts. Because collicular electric stimulation would excite collicular neurons, which in turn send ascending action potentials, it was quite possible that the collicular BF shifts evoked by the collicular electric stimulation were evoked by the corticofugal system. Therefore we also examined whether collicular BF shifts were evoked by the collicular electric stimulation even when the AI was inactivated by a local anesthetic. We found that collicular electric stimulation did not evoke the collicular BF shifts when the ipsilateral AI was inactivated.

METHODS

General

Surgery, acoustic, and electric stimulation, recording of neural activity, and data acquisition, and processing were the same as those described in Ma and Suga (2003). Drug applications to the AI were the same as those described in Ji et al. (2001). The animal studies committee of Washington University in St. Louis approved the protocol for this research.

Twenty adult big brown bats (Eptesicus fuscus) were used. Under neuroleptanalgesia (Innovar 4.08 mg/kg body wt), a 1.5-cm-long
metal post was glued on the dorsal surface of the bat’s skull. A local anesthetic (lidocaine HCl) and an antibiotic (Furacin) ointment were applied to the surgical wound. Three days after the surgery, the awake animal was placed in a body mold, which was hung with an elastic band at the center of a 31°C soundproof room. The metal post glued on the skull was attached to a metal rod with set screws to immobilize the animal’s head. The head was adjusted to face directly at the loudspeaker located 74 cm away. Holes (50–100 μm in diameter) were made in the skull covering the AI and IC on one side. A pair of tungsten-wire electrodes (~7-μm tip diameter, 20–35 μm apart, 1 proximal to the other) was inserted to a depth of 300–1,500 μm in the central nucleus of the IC through one of the holes. The responses (action potentials) of neurons to tone bursts were recorded, and the BF of each neuron was measured. Then this electrode pair was used to electrically stimulate the collicular neurons. A single tungsten-wire electrode (~7-μm tip diameter) was also inserted into the central nucleus of the IC to record the responses of a single neuron to tone bursts and to examine the BF shift of the neuron evoked by electric stimulation of the IC. The distance between the recording and stimulating electrodes was ~450 μm in a horizontal plane and ~300 μm in the vertical plane. The recording electrode was mostly placed 170–200 μm deeper than the stimulating electrodes because BF shifts are largest for neurons with a BF ~5 kHz higher than that of stimulated cortical neurons (Chowdhury and Suga 2000; Ma and Suga 2001a). After the recovery of the shifted BF to the control BF, lidocaine was applied to the ipsilateral AI to inactivate it, and then electric stimulation was again applied to the same collicular neurons stimulated before to examine whether the development of the collicular BF shift evoked by the electric stimulation was affected by cortical inactivation. The second electric stimulation was also delivered to the IC without a lidocaine application to the AI to demonstrate that the effect of lidocaine was not due to the adaptation of the collicular BF shift to the second electric stimulation.

**Acoustic stimulation**

Acoustic stimuli were 5- or 25-ms-long tone bursts with a 0.5-ms rise-decay time because some collicular neurons are tuned to short sounds similar to biosonar pulses (Casseday and Covey 1992; Jen and Zhou 1999) and are corticofugally modulated (Ma and Suga 2001b; Suga and Ma 2003). The tone bursts were delivered at a rate of 5.0/s with a leaf tweeter. First, the frequency and amplitude of the tone bursts were varied manually and the BF and the minimum threshold (MT) of a given collicular neuron were measured. To obtain the frequency-response curve of a neuron, the amplitudes of the tone bursts were fixed at 10 dB above the minimum threshold of the neuron, and the frequencies of the tone bursts were randomly varied by a computer with a stimulus-control and recording software (Tucker-Davis Technologies). This computer-controlled frequency scan consisted of 30 200-ms-long time blocks. In the first 29 blocks, the frequency was changed in 0.1-, 0.2-, or 0.5-kHz steps. In the 30th (last) block, no stimulus was presented to count background discharges. The step size of the frequency scan was determined depending on the sharpness of the frequency-tuning curve of the neuron. An identical frequency scan was repeated 50 times with a 200-ms-long time interval. The amplitudes of the tone bursts were calibrated with a Bruel and Kjaer microphone and were expressed in dB SPL.

**Electric stimulation of the IC**

Electric stimulation delivered to the IC (ESi) was a 6.2-ms-long train of four monophasic electric pulses (100 nA, 0.2-ms duration, 2.0-ms interval). The train of electric stimuli was delivered to the IC at a rate of 10.0/s for 30 min through a constant current stimulus isolator (Model A360 modified by WPI) with the pair of electrodes. Such stimulation was estimated to influence cortical neurons within a 60-μm radius around the electrode tip and to cause a shift of their tuning curves (Yan and Suga 1996). The bat showed no behavioral response at all to such weak electric stimulation.

**Mapping and inactivation of the AI**

On the first day of experiments with a given bat, five to six holes (50–100 μm in diameter) were first made in the skull covering the AI, and the BFs of multiple neurons at these holes were measured to estimate a 30-kHz iso-BF line (the approximate center of the AI) from the distribution of cortical neurons tuned to 20- to 68-kHz sounds sampled at different AI locations. For the estimation, we utilized the map showing the distribution of BFs in the AI of the big brown bat studied by Dear et al. (1993), Jen et al. (1989), and Shen et al. (1997). Then a 1.0-mm-diam hole was made in the skull at the center of the AI for inactivation. The hole was ipsilateral to the electrically stimulated IC. For the inactivation of the AI, 0.5 μl of a 1.0% lidocaine solution was applied to this hole with a 1.0 μl Hamilton syringe. In our experiments, it was clear that lidocaine blocked neural activity in the AI because the collicular BF shift did not develop after lidocaine application to the AI. The duration of the lidocaine effect presumably lasted ≥1.5 h (Zhang et al. 1997).

**Data acquisition**

Action potentials of a single collicular neuron were selected with a time-amplitude window-discriminator software (Tucker-Davis Technologies). The action potential (i.e., template) stored and displayed on the monitor screen was compared with action potentials during data acquisition. The responses of the neuron to a frequency scan delivered 50 times were recorded before and after collicular electric stimulation with or without a lidocaine application to the AI and were displayed as an array of poststimulus time (PST) histograms. The data were acquired between 30 min prior to and ≤420 min after the onset of collicular electric stimulation. The data were stored in the computer hard drive and used for off-line analysis. In a 1-day experiment, only one neuron was studied for the effect of and recovery from collicular electric stimulation without, and then with, a lidocaine application to the AI.

**Off-line data processing**

The data acquired were used for off-line data processing. The magnitude of auditory responses of a given neuron within 50 ms after the onset of tone bursts was expressed by a number of impulses per 50 identical stimuli and was plotted as the function of frequency to show the frequency-response curve of the neuron. A BF was determined as the frequency to which the neuron showed the largest response. Because an identical frequency scan was delivered 50 times, there were 50 samples of BFs that could be used to compute a mean ± SE and to perform statistical analysis. A two-tailed, paired t-test was applied to determine whether the difference in response magnitude between a BF and adjacent frequencies, and between the BFs obtained before and after the electric stimulation and/or drug application, were significantly different for P < 0.05. Both BF shifts and the recovery of BF shifts were significant in all 68 of the 77 collicular neurons studied (paired t-test; P < 0.05). These BF shifts evoked by collicular electric stimulation were highly significant (P < 0.0025) when they shifted back (i.e., recovered) to the BFs in the control condition. Nine neurons of the 77 did not show BF shifts for electric stimulation.

**R E S U L T S**

Of 77 pairs of neurons studied, 53 were studied with 5-ms-long tone bursts and the remaining 24 were studied with 25-ms-long tone bursts. The BF shifts measured with these two types of tone bursts were pooled together because there was no
significant difference between the BF shifts obtained with the 5- or 25-ms-long tone bursts.

**BF shifts of collicular neurons evoked by electric stimulation of nearby collicular neurons**

Electric stimulation of collicular neurons evoked the changes in the auditory responses and frequency-response curves of 68 of the 77 collicular neurons studied. It did not evoke any change in the remaining nine neurons. In the 68 neurons, BF shifts were significant. In Fig. 1, a collicular neuron was tuned to 40.7 kHz (open circles). When 33.0-kHz-tuned collicular neurons were electrically stimulated, the recorded neuron showed a decrease in the response at 40.7 kHz and an increase in the response at 39.3 kHz. As a result of such frequency-dependent changes, the BF of the neuron shifted from 40.7 to 39.3 kHz 30 min after the onset of electric stimulation (filled circles). The BF shifted back (recovered) to 40.7 kHz ~135 min after ES (dashed curve). BFs, BF in the control condition; BFs, BF in the shifted condition. The poststimulus time (PST) histograms on the right display the responses of the neuron to 40.7 (B) or 39.3 kHz (C) obtained before (1, control), 30 min after ES (2), and 135 min after ES (3). The horizontal bars at the bottom show 25-ms-long tone bursts. The BF shift from 40.7 to 39.3 kHz and return both were statistically significant (P < 0.05).

**Relation in BF between stimulated and recorded collicular neurons**

In the 77 pairs of stimulated and recorded collicular neurons, the BFs of stimulated collicular neurons ranged between 19.8 and 68.0 kHz with a mode at 30.5 kHz, whereas those of recorded collicular neurons ranged between 18.3 and 69.0 kHz with a mode at 35.0 kHz. The distribution of these BFs was slightly skewed. The mean and standard error of BFs were 30.5 ± 1.1 kHz for the stimulated neurons and 35.0 ± 1.2 kHz for the recorded ones. The mean difference in BF between paired recorded and stimulated neurons was 4.58 ± 0.62 kHz (n = 77).

Figure 2A shows the distribution of the BFs of recorded and stimulated collicular neurons in the 77 pairs (hereafter, “recorded” and “stimulated” BFs). The recorded and stimulated BFs between 20 and 40 kHz were 69 and 87%, respectively. The ICc of the big brown bat over-represents the frequencies

![Figure 2A](http://jn.physiology.org/)

**FIG. 2.** Distribution of the BFs of recorded and electrically stimulated collicular neurons paired for BF shift measurement (A). The mean and standard error of BFs are 35.0 ± 1.2 kHz (n = 77) for recorded neurons and 30.5 ± 1.1 kHz (n = 77) for stimulated neurons. The mean BF difference between recorded and stimulated neurons were 4.58 ± 0.62 kHz, as shown by the difference between — and - - -; B: BF shifts as a function of the BFs of stimulated neurons. ○, the centripetal BF shifts of the neurons with BFs that were lower than those of paired stimulated neurons. The correlation coefficient (r) for the regression line is 0.85 for A and 0.28 for B.
between 20 and 40 kHz, and neurons tuned to these frequencies have a sharp frequency-tuning curve (Casseday and Covey 1992; Haplea et al. 1994). Therefore the neurons we studied were mostly recorded from this over-representing portion of the ICc. The amount of BF shift showed no tendency that the higher the stimulated BF, the larger the BF shift (Fig. 2B). BF shifts plotted as a function of the BF differences between recorded and stimulated neurons in individual pairs showed a weak tendency that the larger the difference in BF between recorded and stimulated neurons, the larger the BF shift (Fig. 3).

Time courses of BF shifts

The time courses of centripetal and centrifugal BF shifts were studied in 38 of the 59 neurons and 8 of the 9 neurons, respectively. Both the BF shifts appeared to be largest at the end of the 30-min-long electric stimulation and returned (recovered) to the BF in the control condition ~130 min after the electric stimulation (Fig. 4). The means ± SE of recovery time were 125 ± 16 min for 38 centripetal BF shifts and 128 ± 18 min for 8 centrifugal BF shifts. There was no significant different between these two values (t-test, P > 0.1).

Effects of cortical inactivation on the development of collicular BF shifts

Because 12% of the collicular neurons studied showed no BF shifts (Figs. 2 and 3), we first confirmed that collicular electric stimulation evoked the BF shift of a given collicular neuron and then waited for recovery. After waiting an additional 1.5 h, i.e., 240 min after the first electric stimulation of the IC, lidocaine was applied to the ipsilateral AI and the same collicular electric stimulation as the first was repeated. We then found that the collicular BF shift did not develop for the second electric stimulation. Figure 5A shows the mean time course of the centripetal BF shifts of 11 collicular neurons studied as explained in the preceding text. The first electric stimulation of the IC evoked a 0.77 ± 0.17 kHz (n = 11) BF shift, which recovered ~130 min after the onset of the stimulation. The

FIG. 3. BF shifts as a function of differences in BF between paired recorded (ICr) and electrically stimulated collicular neurons (ICS). Of the 77 neurons studied, 59 showed a centripetal BF shift (○ and ◦), 9 showed a centrifugal BF shift (●), and remaining nine showed no BF shift (×). The correlation coefficients (r’s) for the three regression lines range from 0.48 to 0.58.

FIG. 4. The mean time courses of centripetal (○) and centrifugal (●) BF shifts of collicular neurons evoked by electrical stimulation of nearby collicular neurons (ESi). Each symbol and vertical bar indicate a mean ± SE. The number of neurons studied (N) is shown in the figure. ···, the mean time course of the collicular BF shift evoked by cortical electric stimulation (based on Ma and Suga 2001a).
second electric stimulation after cortical inactivation with lidocaine failed to evoke a BF shift that was statistically significant. To demonstrate that this lack of a BF shift for the second electric stimulation was due to neither the adaptation nor habituation of the BF shift, the second electric stimulation was repeated without cortical inactivation. Figure 5B shows that the BF shift evoked by the second electric stimulation was as large as that evoked by the first: $0.79 \pm 0.17$ kHz ($n = 8$) for the first electric stimulation and $0.75 \pm 0.18$ kHz ($n = 8$) for the second.

**Relation between BF shifts and minimum thresholds**

The minimum thresholds (MTs) of recorded and stimulated neurons in the 77 pairs ranged between 2 and 53 dB SPL. The means $\pm$ SE of MTs were $14.8 \pm 0.9$ dB SPL for the recorded neurons and $19.4 \pm 1.2$ dB SPL for the stimulated neurons. MT differences between paired recorded and stimulated collicular neurons ranged between 0 and 38 dB (Fig. 6). The mean $\pm$ SE of MT differences was $-4.5 \pm 1.4$ dB (77). The BF shifts observed were not related to the MT differences (Fig. 6). A BF shift occurred even for a recorded neuron that was different in MT by as much as 38 dB from a stimulated neuron.

**DISCUSSION**

**Comparison of collicular BF shifts evoked by collicular electric stimulation with those evoked by cortical electric stimulation**

The parameters for both 30-min collicular and cortical (Ma and Suga 2001a) electric stimulation were the same. Compared with the collicular BF shifts evoked by cortical stimulation, those evoked by collicular stimulation through the corticofugal feedback (colliculus-to-cortex-to-colliculus) were 37% smaller and 33% shorter-lasting on the average (Fig. 4). The means $\pm$ SE in BF shifts were $0.76 \pm 0.08$ kHz ($n = 38$) for the collicular stimulation and $1.18 \pm 0.10$ kHz ($n = 80$) for the cortical stimulation at the peak which always occurred at the end of the stimulation (Ma and Suga 2001a). This difference was significant ($P < 0.05$). The recovery time of BF shifts was $125 \pm 16$ min ($n = 38$) for the collicular stimulation and $180 \pm 21$ min ($n = 80$) for the cortical stimulation ($P < 0.05$). When the collicular recovery curve was normalized to the cortical recovery curve at the peak, the former becomes the same as the latter. Therefore the difference in recovery time may simply depend on the difference in the amount of a BF shift. The difference in the amount of a BF shift may simply be due to the difference in the magnitude of cortical activation between two stimuli. Namely, the collicular stimulation activates collicular neurons which in turn indirectly activate corticofugal neurons, whereas the cortical stimulation more or less directly activates the corticofugal neurons. Because the neural net is quite...
different between the AI and IC, this difference may also be related to the difference in BF shift as described in the preceding text.

In the AI, the amount of a BF shift is related to the difference between paired recorded cochlear and stimulated cortical neurons (Ma and Suga 2001a). In the present experiments, we also noticed such a relationship. We don’t yet know how the anatomical difference between the AI and IC is related to BF shifts, but it is clear that the collicular BF shift depends on the corticofugal system, not the intrinsic collicular neural net. It should be noted that the collicular BF shift also depends on acetylcholine because it has been demonstrated that atropine (an antagonist of muscarinic acetylcholine receptors) applied to the IC blocks the development of collicular BF shifts (Ji et al. 2001).

In the big brown bat, the “BF shift-difference” curve representing the relationship between BF shifts and BF differences between paired recorded and stimulated neurons is the same for collicular and cortical neurons (Suga and Ma 2003 for review). In the AI, centripetal BF shifts distribute in the area around electrically stimulated cortical neurons, and centrifugal BF shifts distribute in the zone surrounding this area for centripetal BF shifts (Ma and Suga 2004). This center-surround reorganization of the frequency map presumably occurs also in the IC when it is electrically stimulated.

**Collicular BF shifts and multiple feedback loops**

The descending auditory system is complex because it forms multiple feedback loops with the ascending auditory system. Questions remain as to whether the collicular BF shift is partially due to thalamo-collicular projection or whether it is partially due to subcollicular BF shifts elicited by corticofugal and colliculofugal fibers. Because the collicular BF shift did not develop when the AI was inactivated, because the major descending projection to the IC originates from neurons in the cortical layer V (Kelly and Wong 1981), and because the thalamocollicular projection is very minor (Winer et al. 1998), it is unlikely that the thalamo-collicular feedback plays a role in evoking the collicular BF shift observed in our current study. The colliculofugal neurons may be activated by the electric stimulation of the IC directly or indirectly, i.e., through the cortico-collicular feedback, and may evoke BF shifts of subcollicular neurons. As shown in Fig. 5A, the collicular BF shift was not evoked by focal electric stimulation of the IC when the AI was inactivated. Therefore we may conclude that the BF shift evoked by the collicular electric stimulation in our experiment did not evoke subcollicular BF shifts that might consequently be carried up to the IC.

An electric pulse of 0.2 ms and 100 nA at a rate of 5.0/s for 7.0 min (Zhang and Suga 2000) or a 6.2-ms-long train of four electric pulses (0.2 ms-long, 100 nA, 2.0-ms interval) at a rate of 10.0/s for 30 min (Ma and Suga 2001a) delivered to the AI evokes cortical, thalamic and collicular BF shifts but does not evoke subcollicular BF shifts (Xiao and Suga 2002). This does not mean at all that the corticofugal system cannot evoke BF shifts at the subcollicular nuclei and cochlear hair cells because it has been found that the BF shift of cochlear hair cells is evoked by a train of electric stimulation delivered to the AI at a rate of 33/s for 3.0 min but not by a single electric pulse stimulation delivered to the AI at a rate of 5.0/s for 7.0 min (Xiao and Suga 2002). It is likely that subcollicular BF shifts are evoked as collicular electric stimulation is increased in intensity and/or repetition rate.

**Ipsi- versus contralateral corticofugal modulation**

Corticocollicular fibers bilaterally project to the IC (Andersen et al. 1980; Feliciano and Potashner 1995; Herrera et al. 1994; Saldana et al. 1996). The ipsilateral projection is much heavier in density, much more extensive in the projecting area, and much more topographically organized than the contralateral projection (Herbert et al. 1991; Winer et al. 1998). It has also been demonstrated that ipsilateral corticofugal modulation is larger than contralateral corticofugal modulation in the IC (Ma and Suga 2001a). In our current studies, inactivation of the ipsilateral AI abolished the development of the collicular BF shift. It is thus clear that the ipsilateral corticocollicular projection predominates in evoking the collicular BF shift.

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