Corticofugal Amplification of Subcortical Responses to Single Tone Stimuli in the Mustached Bat

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Zhang, Yunfeng and Nobuo Suga. Corticofugal amplification of subcortical responses to single tone stimuli in the mustached bat. J. Neurophysiol. 78: 3489–3492, 1997. Since 1962, physiological data of corticofugal effects on subcortical auditory neurons have been controversial: inhibitory, excitatory, or both. An inhibitory effect has been much more frequently observed than an excitatory effect. Recent studies performed with an improved experimental design indicate that corticofugal system mediates a highly focused positive feedback to physiologically “matched” subcortical neurons, and widespread lateral inhibition to “unmatched” subcortical neurons, in order to adjust and improve information processing. These results lead to the question: what happens to subcortical auditory responses when the corticofugal system, including matched and unmatched cortical neurons, is functionally eliminated? We temporarily inactivated both matched and unmatched neurons in the primary auditory cortex of the mustached bat with muscimol (an agonist of inhibitory synaptic transmitter) and measured the effect of cortical inactivation on subcortical auditory responses. Cortical inactivation reduced auditory responses in the medial geniculate body and the inferior colliculus. This reduction was larger (60 vs. 34%) and faster (11 vs. 31 min) for thalamic neurons than for collicular neurons. Our data indicate that the corticofugal system amplifies collicular auditory responses by 1.5 times and thalamic responses by 2.5 times on average. The data are consistent with a scheme in which positive feedback from the auditory cortex is modulated by inhibition that may mostly take place in the cortex.

INTRODUCTION

Neurons in the deep layers of the auditory cortex (AC) project to the medial geniculate body (MGB) or to the inferior colliculus (IC) (Huffman and Henson 1990; Saldana et al. 1996). The corticofugal projections are tonotopically organized (Andersen et al. 1980; Herbert et al. 1991). Physiological data of corticofugal effects on the MGB and IC neurons have been controversial: inhibitory (Amato et al. 1969; Massopust and Ordy 1962; Sun et al. 1996; Watanabe et al. 1966), excitatory (Andersen et al. 1972; Villa et al. 1991), or both (Ryugo and Weinberger 1976; Sun et al. 1989; Syka and Popelar 1984). These studies did not reveal the functional role of the corticofugal projections because of limitations in experimental design.

The recent findings made in the AC of the mustached bat, Pteronotus parnellii parnellii, indicate that cortical neurons mediate a highly focused positive feedback, incorporated with widespread lateral inhibition, via corticofugal projections. Therefore an inhibitory or excitatory corticofugal effect depends on a topographic relationship between cortical and subcortical neurons (Yan and Suga 1996; Zhang et al. 1997). In cats, He (1997) found corticofugal effects similar to the above.

However, Sun et al. (1996) reported that in the big brown bat, Eptesicus fuscus, the corticofugal pathway modulates auditory responses of collicular neurons only by inhibition. If they are correct, a large cortical inactivation should eliminate inhibition in the IC and should increase collicular auditory responses. However, if the excitation due to positive feedback, found in the mustached bat, is larger than lateral inhibition, a large cortical inactivation should decrease the auditory responses of subcortical neurons. The aim of the present study is to measure the total amount of change produced by the corticofugal system by entirely inactivating the corticofugal fibers originating from a particular subdivision of the primary auditory cortex, called the Doppler-shifted constant-frequency (DSCF) processing area.

The DSCF area is ~1.4 mm diam and consists of neurons sharply tuned to sounds between 60.6 and 62.3 kHz (Suga and Manabe 1982; Suga et al. 1987). For frequencies between 61.0 and 61.5 kHz, best frequency shifts at a rate of ~66 Hz per cortical minicolumn, which is ~20 μm wide. DSCF neurons tuned to a particular frequency augments the auditory responses of thalamic and collicular neurons (hereafter, subcortical neurons) tuned to the same frequency (not different by >0.2 kHz), and reduce the responses of subcortical neurons tuned to other frequencies (different by >0.2 kHz). This means that single subcortical neurons receive positive feedback from one or a few cortical minicolumns, and receive lateral inhibition from many, perhaps, all other minicolumns in the DSCF area (Zhang et al. 1997). We found that inactivation of both matched and unmatched cortical DSCF neurons evokes a prominent decrease in subcortical auditory responses.

METHODS

Materials, surgery, recording of neural activity, acoustic stimulation, and data acquisition were basically the same as those described elsewhere (Suga et al. 1983). The essential portions of these are summarized below. Four adult mustached bats (Pteronotus parnellii parnellii) were used for the present experiments. Under neuroleptanalgesia (Innovar 4.08 mg/kg body wt), the dorsal surface of the bat’s skull was exposed, and a 1.8-cm-long metal post was glued onto the skull. Four days after the surgery, the anesthetized bat was placed in a styrofoam restraint suspended by an elastic band at the center of a soundproof, echo-attenuated room maintained at 30–32°C. The head was immobilized by fixing the post on the skull to a metal rod with set screws, and adjusted directly at a condenser loudspeaker located 74 cm away. “DSCF” neurons are tuned to 60.6 to ~62.3 kHz sounds and are clustered in the DSCF area of the AC, the ventral division of the MGB, and the dorsoposterior division of the IC. To record their auditory
responses, a tungsten-wire microelectrode was inserted into one of these structures through holes of ~50 μm diam made in the skull. DSCF neurons were identified by their best frequencies (BFs) and locations in the AC, MGB, and IC. A window discriminator was used to isolate action potentials of single neurons.

The acoustic stimuli were 23-ms-long tone bursts with a 0.5-ms rise-decay time. These were generated by a voltage-controlled oscillator and an electronic switch and were delivered at a rate of 5/s. The frequency of a tone burst was varied manually or by a computer. Collicular, thalamic, and cortical DSCF neurons were tuned to particular frequencies (BFs), and particular amplitudes (best amplitudes). The amplitudes of the tone bursts of a computerized frequency (F) scan were set at the best amplitude of a given neuron, which was usually ~30 dB above minimum threshold.

The F scan consisted of 21 time blocks, in 20 blocks of which frequency was changed in 0.10-kHz steps. In the 21st (last) block, no stimulus was presented in order to count background discharges. The duration of each block was 200 ms, so that the duration of the F scan was 4,200 ms. The F scan was used to obtain a frequency-response curve (Fig. 3). To measure the time course of a change in subcortical auditory responses evoked by cortical inactivation (Fig. 2), a modified F scan was used in which the frequency of tone bursts was fixed at the BF of the subcortical auditory neuron under study.

After mapping the DSCF area, a hole of 0.2–0.3 mm diam was made in the skull at the center of the DSCF area, and a well was placed over the hole. A few days later, single subcortical DSCF neurons were recorded, and 0.2 μg muscimol (1.0 μg/μl saline) was applied to the DSCF area with a 1.0-μl Hamilton microsyringe to inactivate the DSCF area. Gelfoam (gelatin sponge) was placed in the well to prevent leakage of muscimol and to increase the contact time with the cortical surface. To study the effect of cortical inactivation on the auditory responses of subcortical neurons, the responses of single subcortical neurons to tone bursts in the F or modified F scan were recorded with a computer before, during, and after the cortical inactivation. The F or modified F scan was delivered once every 5 s during data acquisition.

Off-line data processing included plotting peristimulus time (PST) and PST cumulative (PSTC) histograms displaying the responses to 50 identical acoustic stimuli. Frequency-response curves were based on the responses to 50 identical F scans. The magnitude of auditory responses was expressed by the number of impulses per 50 identical stimulus blocks after subtracting background discharges counted in the last block of the F or modified F scan repeated 50 times. The t-test was used to test the significance of the difference between the auditory responses obtained before and after muscimol application, and between the responses of thalamic and collicular neurons.

**Results**

The effect of inactivation of the DSCF area with muscimol was studied for five thalamic and six collicular DSCF neurons. The sample size was small because of the difficulty in obtaining a long-term recording of single-unit activity. Nevertheless, the results were consistent. Cortical inactivation reduced the auditory responses of every subcortical neuron studied and evoked no change in its BF. Figure 1 shows such reduction in the auditory responses of a thalamic (A) and a collicular neuron (B). The amount of the reduction was larger for the thalamic neurons than for the collicular neurons. Both the initial and later portions of the response were reduced by approximately the same amount. Figure 2 shows the time courses of muscimol’s effect on auditory responses and background discharges of a thalamic (A) and a collicular neuron (C), and the average time courses for the five thalamic (B) and six collicular neurons (D).

After muscimol application, the reduction in auditory response for the thalamic neurons began simultaneously with that of the collicular neurons. However, the reduction in responses developed faster [11 ± 4.2 (SD) min vs. 31 ± 15 min for 1/2 of the maximum decrease] and was larger (60 ± 35% vs. 34 ± 7.8% at the maximum decrease) for the thalamic neurons than for the collicular neurons. This result indicates that, normally, auditory responses are amplified by the corticothalamic projection and are further amplified by corticocollateral projection. The latency and duration of the plateau reduction (plateau reduction is defined as the reduction to within 10% above the maximum reduction) and the latency of 50% recovery were almost the same for the thalamic and collicular neurons.

Background discharge rates ranged between 1.0 and 4.2/s (3.3 ± 0.87/s, n = 5) for the thalamic neurons and between 1.4 and 3.9/s (3.2 ± 0.75/s, n = 6) for the collicular neurons. Muscimol application evoked a large reduction in background discharges of all thalamic neurons. The mean and standard deviation of percent reduction are 75 ± 9.3%, n = 5 (Fig. 2, A and B). Muscimol application evoked no sig-

**FIG. 1.** Decrease in the auditory responses of a thalamic (A) and a collicular neuron (B) evoked by a large cortical inactivation, including “matched” cortical neurons, with muscimol. Each peristimulus-time (PST) histogram displays the responses of a single neuron to 50 identical stimuli. These responses were recorded before (a: control condition), during (b: muscimol), and after (c: recovery condition) the inactivation. The acoustic stimulus (tone burst) was a 60.98 kHz, 45 dB SPL for A and a 61.08 kHz, 47 dB SPL for B. Horizontal bars below the histograms indicate 23-ms-long acoustic stimuli. The PST histograms in a–c are also shown by the PST cumulative (PSTC) histograms in d. MGB, medial geniculate body; IC, inferior colliculus.
significant reduction in three of the six collicular neurons (Fig. 2C), but a significant reduction in the remaining three (35 ± 22.3%, n = 3, P < 0.05). The mean reduction for all six collicular neurons was insignificant (Fig. 2D).

The reduction in auditory response by muscimol applied to the DSCF area was larger and faster for thalamic neurons than for collicular neurons. Therefore one may consider a possibility that muscimol applied to the AC diffused to the MGB and IC. Muscimol applied to the FM-FM area, which is located immediately dorsoanterior to the DSCF area, reduced the auditory responses of thalamic FM-FM neurons (J. Yan and N. Suga, unpublished observations), but did not at all reduce the responses of three thalamic and one collicular DSCF neuron tested. Muscimol applied to the DSCF area had no effect on thalamic FM-FM neurons, which were located immediately dorsomedial to thalamic DSCF neurons. These control experiments indicate that the effect of muscimol described in the present paper was due to the inactivation of the corticofugal system originating from the DSCF area. Also, the fact that reduction in responses of thalamic and collicular neurons began simultaneously argues in favor of a corticofugal effect, rather than a diffusion of muscimol to each subcortical nucleus.

The absolute amount of reduction by muscimol was largest for the responses to the tone burst at the BF of a given subcortical DSCF neuron, but the reduction expressed as a percentage was similar to all the responses to tone bursts at the BF and at other frequencies (Fig. 3). In the present study, all frequency-response curves were obtained at the best amplitude to excite a given subcortical neuron that was, on the average, 29 ± 6.7 dB above minimum threshold for the five thalamic neurons, and 30 ± 5.4 dB above minimum threshold for the six collicular neurons. The 50% bandwidths of the frequency-response curves showed no change >0.1 kHz for all subcortical neurons studied, except for one collicular neuron.

**Discussion**

The dose of muscimol we applied to the DSCF area is known to evoke a prominent temporary deficit in frequency discrimination within a frequency range of 60.6 and 62.3 kHz, but no deficit in echo-delay (time interval) discrimination (Riquimaroux et al. 1991). Therefore this dose of muscimol presumably inactivated the whole DSCF area, and we infer that without the corticofugal system, responses to single tone bursts would be ~60 and 34% less than normal at the MGB and IC, respectively.

A reduction of auditory responses evoked by a focal inactivation of cortical DSCF neurons with 90 ml of 1.0% lidocaine is 54 ± 15% (n = 4) for matched thalamic neurons and 21 ± 8.9% (n = 4) for matched collicular neurons (Zhang et al. 1997). We expected that the reduction of auditory responses evoked by the large cortical inactivation with muscimol would be larger than these. The reduction was indeed larger for collicular neurons [34 ± 7.8% (n = 6) vs. 21 ± 8.9% (n = 4); P < 0.05], but not for thalamic neurons [60 ± 35% (n = 5) vs. 54 ± 15% (n = 4); P > 0.1]. It remains to be studied whether this is due to less convergence in the corticothalamic pathway than in the corticocollicular pathway.

In the big brown bat, collicular auditory responses are strong, so that these responses are attenuated (modulated) in the IC by corticofugal inhibition (Sun et al. 1996). Similar data have also been obtained from cats (Amato et al. 1969; Massopust and Ordy 1962; Watanabe et al. 1966). Because of the findings by Yan and Suga (1996) and Zhang et al. (1997), we can offer two explanations as to why Sun et al. (1996) and others observed only an inhibitory corticofugal effect. 1) Positive feedback is highly focused to matched subcortical neurons, so that it is unlikely to be observed without first identifying matching cortical and subcortical re-
Lateral inhibition is widespread over, presumably, all unmatched neurons within a given cortical subdivision (e.g., the 1.4-mm² DSCF and the 0.9-mm² FM-FM area), so that electrical stimulation of the AC evokes a decrease in the auditory responses of most subcortical neurons, and lidocaine applied to the AC evokes an increase in the responses of most subcortical neurons. Our interpretations are supported by the data obtained from the cat: inactivation of almost all of the AC by cooling reduced the auditory responses of MGB neurons (Villa et al. 1991). The difference between our data and those of Sun et al. is unlikely to be due to a species difference, because Yan and Suga (unpublished observations) have obtained the data indicating that cortical auditory neurons of the big brown bat share identical corticofugal mechanisms with those of the mustached bat.

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