Corticofugal Modulation on Both ON and OFF Responses in the Nonlemniscal Auditory Thalamus of the Guinea Pig

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He, Jufang. Corticofugal modulation on both ON and OFF responses in the nonlemniscal auditory thalamus of the guinea pig. J Neurophysiol 89: 367–381, 2003. 10.1152/jn.00593.2002. Corticofugal modulation on both ON and OFF responses in various nuclei in the medial geniculate body (MGB) was examined by locally activating the auditory cortex and looking for effects on the neuronal responses to acoustic stimuli. In contrast with a major corticofugal facilitatory effect on the ON neurons in the lemniscal nucleus of the MGB of the guinea pigs, of 132 ON neurons tested in three conditions with cortical activation through each of three implanted electrodes, the majority of the tested conditions (319/396) that were sampled from the nonlemniscal nuclei of the MGB received inhibitory modulation from the activated cortex. This inhibitory effect was >50% for 99 cases while the auditory cortex was activated. Most of the OFF and ON-OFF MGB neurons (44/54) showed a facilitatory effect of 111.4 ± 99.9%, and three showed a small inhibitory effect of 25.7 ± 5.8% on their OFF responses. Thirty neurons in the border region between the lemniscal and nonlemniscal MGB showed mainly facilitatory corticofugal effects on both ON and OFF responses. Meanwhile, cortical stimulation induced almost exclusive inhibitory effects on the ON response and facilitatory effects on the OFF response in the MGb. It is suggested that the OFF response is produced as a disinhibition from the inhibitory input of the auditory stimulus. The present results provide a possible explanation for selective gating of the auditory information through the lemniscal MGB while switching off other unwanted sensory signals and the interference from the limbic system, leaving the other auditory cortex prepared to process only the auditory signal.

INTRODUCTION

The thalamus relays ascending information to the cortex and in turn receives a much stronger reciprocal projection than the ascending information from the cortex to the thalamus (Andersen et al. 1980; Montero 1991; Liu et al. 1995a; Ojima 1994). Cortical feedback to the thalamus has been suggested as to provide a gating or gain-control mechanism in the transmission of information from the periphery to the thalamus (Crick 1984; Deschênes and Hu 1990; Murphy and Sillito 1987; Sherman and Koch 1986).

Earlier studies using technique by Ryugo and Weinberger (1976) and Villa et al. (1991) have demonstrated that the auditory cortex has two processes for modulating its thalamic relay nucleus: facilitatory and inhibitory. Most recently, investigators have used electrical currents to activate the cortex rather than cooling the brain, which has already been depressed to some degree by the anesthesia (Ryugo and Weinberger 1976; Suga et al. 1997; Villa et al. 1991; Zhou and Jen 2000). Electrical activation of the auditory cortex caused mainly strong facilitation and little inhibition on the lemniscal nucleus, i.e., the ventral nucleus (MGv), of the cat medial geniculate body (MGB), of which it was suggested that the facilitation was generated via the corticothalamic terminals and the inhibition through the activation of interneurons (He 1997; He et al. 2002). The corticofugal inhibitory effect has also been observed in the MGBs of the cat and bat (Amato et al. 1969; Suga et al. 1997; Watanabe et al. 1966; Yan and Suga 1999). Consisting of the shell (MGs), the caudomedial (MGcm), and rostromedial (MGrm) nuclei, the nonlemniscal MGB showed long latency, a bursting firing pattern, broad/nontuning properties, and nontonotopic organization and was found to be an integrative system involving multi-sensory afferents (Calford and Aitkin 1983; He and Hashikawa 1998; He and Hu 2002; He et al. 1997; Hu 1995; Rauschecker et al. 1997; Wepsic 1966; Winer and Morest 1983; Winer et al. 1992, 1999). The magnocellular division of the nonlemniscal MGB, which is equivalent to the MGcm of the guinea pig, also projects to and receives input from the amygdala and the basal ganglia (Cruikshank et al. 1992; LeDoux et al. 1990; Shinonaga et al. 1994; Wepsic and Sutin 1964). Recently we found that the ON and OFF pathways are segregated in the MGB. The OFF and ON-OFF neurons tend to be located on the border region between the lemniscal and nonlemniscal nuclei or beyond the lemniscal nucleus, respectively (He 2001, 2002). It will be interesting to compare the corticofugal modulatory effects between the lemniscal and nonlemniscal nuclei and between the ON and OFF responses. In our pilot study on the cat MGB, strong corticofugal inhibitory effects on the ON response were observed in the nonlemniscal MGB, for which three possible causes can be identified: thalamic interneurons, reticular nucleus (RTN) neurons, and inferior collicular (IC) GABAergic neurons, which project directly onto the MGB (Winer et al. 1996).

To exclude the first possibility, we shifted in the present study to a simpler animal model, the guinea pig with a very few thalamic interneurons (Arcelli et al. 1997). The corticofugal modulatory effect on the thalamic neurons of the guinea pig was mapped in the frontal or parasagittal planes at various locations, enabling us to make a comparison between the different nuclei of the MGB.

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Methods

Animal preparation

Fifteen adult guinea pigs with clean external ears served as subjects, with normal auditory thresholds estimated from the cortical unit responses. Ketamine/xylazine (40 and 10 mg/kg initially, 10 and 2.5 mg · kg⁻¹ · h⁻¹) was administered during the surgical preparation and recording. Atropine sulfate (0.05 mg/kg sc) was given 15 min before anesthesia and at regular intervals (0.01 mg · kg⁻¹ · h⁻¹) during the recording to inhibit tracheal secretion. The preparation of the guinea pig is similar to that of the cat and another recent study of the guinea pig and has been described before (He 1997, 2001). Briefly, the subject was mounted in a stereotaxic device after the induction of anesthesia. A midline incision was made in the scalp, and craniotomies were performed to enable us to map the auditory cortex, to implant stimulation electrodes into it, and to vertically access the MGB in the left hemisphere. The dura mater was removed above the auditory cortex and at a position vertically above the auditory thalamus. The head was fixed with two stainless steel bolts to an extended arm from the stereotaxic frame using acrylic resin, before the right ear was freed from the ear bar, so that the subject’s head remained fixed to the stereotaxic device without movement. The procedures were approved by the Animal Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University.

Acoustic stimulus

Acoustic stimuli were generated digitally by a MAIab system (Kaiser Instruments, Irvine, CA), which was controlled by a Macintosh computer (He 1997; Semple and Kitzes 1993). Acoustic stimuli were delivered to the subject via a dynamic earphone (Bayer DT-48) mounted in a probe. The subject was placed in a double-walled soundproof room (NAP, Clayton, Australia). Repeated noise bursts and pure tones with intervals of ≥1 s and 5-ms rise/fall time were used to examine the neuronal responses.

Recording

Tungsten microelectrodes with impedances of 9–12 MΩ (Frederick Haer, Brunswick, ME) were advanced by a stepping-motor microdrive, which was controlled outside the soundproof room. The time of spike occurrence relative to stimulus delivery was stored in the same computer as the stimulus controller by the MAIab software. The computer automatically created raster displays and peristimulus time histograms of the responses, together with frequency response functions (responses to pure tones plotted as a function of frequency).

The tonotopicity of the auditory cortex for each subject was mapped to identify the electrical stimulation sites for the later experimental sessions. To characterize the auditory cortex, we used 50-ms tone pips (5-ms rise/fall time, >400-ms interval) and most often recorded spikes from cell clusters rather than single cells.

The MGB was accessed vertically from the top of the brain in the stereotactically positioned subject, according to a guinea pig brain atlas (Rapisarda and Bacchelli 1977). The vertical coordinate of the electrode was determined at a point slightly above the cortical surface at the first penetration. A single electrode was used for each experiment so that the depth coordinates could be kept consistent for different penetrations during the experiment. This technique enabled us to reconstruct the physiological map of the whole sagittal or frontal auditory thalamic plane containing many penetrations, and to superimpose it with the Nissl staining. Pure tones and noise bursts were used as testing acoustic stimuli. We intended to record from single units in the MGB while measuring the modulatory effects of cortical activation.

Electrical stimulation

After a rough mapping of the auditory cortex, three electrodes were implanted into the auditory cortex targeting the anterior (A, 38 stimulation electrodes over 14 roughly mapped cortex) and the dorsocaudal (DC, 4 stimulation electrodes) fields, to which the MGv projects and from which it assumptively receives reciprocal projections (Redies et al. 1989). The stimulation electrodes were in a rostrocaudal row and separated by ~0.5–1.0 mm from each of their neighbors.

We used electrical current pulse trains of 0.1-ms width, 100- to 200-Hz frequency, and 30 pulses to activate the auditory cortex. Biphasic pulse trains of electrical current of 50–1,000 μA, delivered by an isolator, were applied to the auditory cortex ipsilaterally to the recording thalamus through bi-polar low-impedance electrodes (glass-shielded tungsten microelectrodes with their tips exposed). We examined the effective current threshold of the corticofugal effect and its dependence on the current intensity for 15 neurons.

For standard statistics, of 287 neurons presented in the present report, 56 neurons were tested under a stimulation current of 100 μA and 231 neurons under 200 μA. The electrodes were placed at 1,000 μm under the surface of the cortex, aiming at layer VI of the cortex. A sound stimulus was delivered to the contralateral ear of the recording hemisphere after the end of the cortical stimulation, after a delay interval of 100 ms (He 1997). The responses of the thalamic neurons to pure tones and noise bursts were compared with and without cortical activation.

Data collection and analysis

The responses of the thalamic neurons to a certain acoustic stimulus were examined in the control condition, i.e., without electrical activation of the cortex, before (E-b) and after (E-a) the experimental conditions, which included the sequential activations of three stimulation electrodes in the cortex in a pseudorandom order (EX, EY, and EZ). The neuronal responses in the experimental conditions were compared with those in the control condition. The responses of most ON and OFF neurons were counted for 50 ms starting from the onset or the offset time. There were exceptional: for tonic responses we counted the whole stimulus on time, and for some long-latency ON or OFF responses, we counted for 100 ms. To eliminate artifacts due to fluctuations in neuronal responsiveness over time due to uncontrolled variables, neurons that showed >15% change in the spike numbers in condition E-a over E-b were excluded from the data analysis.

Anatomical confirmation

Eight subjects were used for the purpose of anatomical confirmation. A small lesion (1.0 μA, 20 s) was made on two animals through passing a current into the recording electrode (9–12 MΩ) at the last recording site in the MGB. They were deeply anesthesitized with pentobarbital sodium and perfused transcardially with 0.9% saline followed by a mixture of 0.4% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.3). The brains were removed and stored overnight in 0.1 M phosphate buffer containing 30% sucrose. The thalami were cut transversally into 40-μm-thick sections using a freezing microtome.

The sections were stained using the Nissl method. The Nissl sections were superimposed with the physiology map, using the electrode penetration tracks and the lesion for guidance. There was some shrinkage of the sections after the Nissl procedure. Enlargements of 10–13% of the Nissl images were made to match them to the physiology maps.

Results

MGB of the guinea pig

The MGB of the guinea pig has been divided into the MGv, the MGs, the MGcm, and MGmr (He 2001; Redies and Brand-
ner 1991; Redies et al. 1989). We confirmed in the present study that the organization of the characteristic frequencies is well matched with that of previous investigators: high frequencies were located rostrally, intermediate frequencies in the center rostrocaudally, and low frequencies caudally (Redies and Brandner 1991). It was confirmed in the present study that many OFF or ON-OFF neurons were located on the border between the lemniscal and nonlemniscal nuclei or in the nonlemniscal nuclei of the MGB (He 2001).

Corticofugal modulation on the ON neurons

Of 233 ON neurons examined in 15 subjects, 101 were sampled from the MGv, 36 from the MGs, 68 from the MGcm, and 28 from the MGrm of the MGB. Because the main focus of the present report is on the nonlemniscal MGB, only a brief description of the MGv is presented here. We tested each of 101 MGv neurons over three conditions, in each of which one of the implanted electrodes was activated using a moderate electrical current (100–200 μA). Of 303 cases (101 neurons × 3 stimulation sites) tested, 208 showed a facilitatory effect, 85 showed no effect, and only 10 showed an inhibitory effect. Among the cases of facilitation, 63 cases showed a facilitatory effect >100%, and 145 cases showed an effect from 20 to 100%. Detailed information has been published elsewhere (He et al. 2002).

Most of the neurons in the nonlemniscal nuclei of the MGB showed an inhibitory effect while the cortex was activated at any of the three sites. Three examples are shown in Fig. 1, in which the neurons showed decreased firing rates while any of the three sites in the auditory cortex: X, Y, and Z, was electrically activated. Compared with the control condition, E-b, the neurons showed no change in the firing rate for another control after the experimental trials: EX, EY, and EZ, as shown

![Corticofugal modulation on the ON neurons](attachment:image)

**FIG. 1.** Effects of cortical activation on the non-lemniscal medial geniculate body (MGB) neurons. Raster displays show three typical examples of neuronal responses to repeated noise bursts while different sites in the auditory cortex were electrically activated: A: a shell nucleus (MGs) neuron; B: a caudomedial nucleus (MGcm) neuron; and C: a rostromedial nucleus (MGrm) neuron. Noise burst was repeated over 19 trials at 1.0-s intervals for each condition. E-b and E-a, control conditions taken before or after the experimental conditions for which only acoustic stimulus was given to the subjects; EX, EY, and EZ, experimental conditions for which an electrical stimulation was applied to the auditory cortex at 1 of 3 different sites prior to the acoustic stimulus. Only onsets of 100–200 ms of the responses were shown in the figure. The time interval (Δt) between the electrical stimulation and the acoustic stimulus was 100 ms. Inset: experimental paradigm. The conventions apply to Figs. 3, 5, and 9–11.

![Cortico-fugal modulation on ON neurons](attachment:image)

**FIG. 2.** Numbers and proportions of ON neurons receiving facilitatory and inhibitory corticofugal effects in each nucleus of the MGB. Top: the number of neurons; bottom: the proportion of the facilitatory (F) and inhibitory (I) type neurons. In the calculation, we counted the neurons which showed facilitatory effects for ≥2 sites over the 3 implanted electrodes in the cortex as F type, those showing inhibitory effects for ≥2 sites as I type, and all other patterns as unclassified (U) type.
in E-a. The neuron in Fig. 1B was completely shut off while site Y or Z was activated. Of 108 cases (36 × 3) sampled in the MGs, 83 showed an inhibitory effect, 20 showed no effect, and only 5 showed a facilitatory effect. Among the 83 inhibitory cases, 15 showed a strong effect of >50% inhibition, including 5 cases in which the neuronal responses to acoustic stimulus were completely suppressed. Of the 204 cases (68 × 3) tested in the MGcm, 174 showed an inhibitory effect (20–50% inhibition).
bition for 100 cases, >50% for 74 cases, including 33 cases of total suppression), 27 showed no effect, and 3 showed a facilitatory effect. Of the 84 cases (28 × 3) tested in the MGm, 62 showed an inhibitory effect: 20–50% inhibition for 52 cases, >50% for 10 cases, including 5 cases of total suppression.

A comparison of the facilitatory and inhibitory effects of the corticofugal modulation on the neurons in various nuclei of the MGB is shown in Fig. 2. In the calculation, we counted the neurons which showed facilitatory effects for two sites or more (/3) as the facilitatory (F) type, those which showed inhibitory effects for two sites or more as the inhibitory (I) type and all other patterns as the unclassified (U) type.

The proportions of the neurons of the F and I types over the total number of neurons in each nucleus are shown in Fig. 2. Comparing with the overall corticofugal facilitation on the MGv (70% were F type neurons and only 1% were I type neurons), the corticofugal modulation on other nuclei was mainly inhibitory (≤54% F type neurons and ≤80% I type neurons). The inhibitory modulation was most obvious in the MGcm, where only 1% neurons were of the F type and 88% were of the I type.

Parameters of the stimulation current

As mentioned in a previous report (He 1997), the stimulation current is an important parameter. We have examined this parameter on 20 nonlemniscal neurons. A stronger inhibitory effect was obtained for most neurons when the stimulation current was increased from a few hundred microampere to 500 μA or 1 mA as in the example shown in Fig. 3A.

The neuron in Fig. 3A showed a small decrease of 20% when the stimulation current was 70 μA. The inhibitory effect was greatly strengthened to 78 and 87% when the current was increased to 700 μA and 1 mA, respectively.

A few neurons showed complicated patterns responding to the increment of the stimulation current, as in one example shown in Fig. 3B. The effective current of electrical stimulation was ~50 μA, as shown in Fig. 3B, first row. Inhibitory effects of 27 and 29% could be detected while sites Y and Z were activated by this current but not in the case of site X. This inhibitory effect became stronger when the current was increased to 100 μA: 62% for site Y and 60% for site Z. However, it became weaker when the stimulation current was further increased to a range of 200–400 μA. It again became stronger and was at its strongest when we further increased the stimulation current to >700 μA. Two controls shown on both sides of Fig. 3B, which were carried out before and after each current intensity, indicated a stable recording for the whole session.

The effect of the stimulation current was tested on eight nonlemniscal neurons, which showed the inhibitory effect of cortical stimulation. Because some of them were tested for two or three different stimulation sites in the cortex, we obtained 19 examples in total for the current effect function, as shown in Fig. 3C. It is a general trend that the inhibitory effect becomes stronger when the stimulation current is enlarged for all the neurons (Fig. 3C, left), though some samples (Fig. 3C, right) show fluctuation at some current intensity similar to the example in Fig. 3B.

The interstimulus interval (Δt) between the electrical and acoustic stimuli as defined in Fig. 1 was also tested as a parameter in the nonlemniscal neurons of the present study and the lemniscal neurons of previous studies (He 1997; He et al. 2002). Figure 4 shows an example of an MGcm neuron tested with 100-μA activation of the cortical field A. The Δt was changed from 30 to 300 ms, and the most effective Δt ranged from 50 to 150 ms.

Neurons in MGcm

After the stimulation electrodes were implanted in a characterized cortex, we mapped the modulatory effects of the auditory thalamus frontally or parasagittally. Figures 5 and 6 show three samples at the caudal part of the MGB in which the MGcm and partial MGv were included.
Using Rapisarda and Bacchelli’s (1977) coordinate, the rostrocaudal coordinate of the sampled plane in Fig. 5A was 3.8 mm, and the plane was located at about a quarter of the MGB from the caudal pole of it. Recorded neurons in the MGcm received mainly corticofugal inhibitory effects. Two neurons in the MGs received also inhibitory effects, while a neuron in the MGv received a facilitatory effect from the site X (low frequency) and no effects from other stimulation sites (high frequencies). The partial parasagittal plane shown in Fig. 5B was located in the caudal half of the MGB and was perpendicular to the frontal plane in A. The plane was at the mediolateral coordinate of ML = 4.2 mm. The caudorostral coordinate is shown above the map, and the depth coordinate is shown on the left. Inset: the best frequencies (BFs) of the stimulation sites in the auditory cortex. C and D: the responses of 2 neurons were sampled from 2 sites: 1 from the MGcm and the other from the MGv. They are shown in raster displays (C) and PSTHs (D). closed circles, the inhibitory effects of cortical activation on the thalamic neurons at the illustrated site; open circles, facilitatory effects; ×, no effect. For closed circles, the smaller ones indicate inhibitory effects between 20 and 50%, and the bigger ones those between 51 and 100%. For the open circles, the smaller ones indicate facilitatory effects between 20 and 100%, and the bigger ones those >100%. W, weak response to noise burst; N, no response to noise burst; L, response to noise burst with a latency longer than 50 ms; OFF, off response to auditory stimulus; ON-OFF, ON and OFF responses to auditory stimulus; Numbers in parentheses indicate the best frequency of the neuron in the recording site. These conventions apply to Figs. 6–8. Bar, 1 mm.

FIG. 5. Modulatory effects of cortical activation on the caudal part of the MGB. A: a frontal plane for physiological study was sampled at the caudal part of the MGB. A Nissl staining of the sampled location was superimposed on the physiological map (left). Modulatory effects caused by activation at different sites of the auditory cortex: X, Y, and Z were illustrated, as indicated, as EX, EY, and EZ. Using Rapisarda and Bacchelli’s (1977) coordinate, the plane was at the rostrocaudal coordinate of RC = 3.8 mm. The mediolateral coordinate is shown above the map, and the depth coordinate is shown on the left. The depth coordinate was initiated at the 1st penetration and remained the same during the whole mapping process. B: a partial parasagittal plane was sampled from the caudal half of the MGB and was perpendicular to the frontal plane in A. The plane was at the mediolateral coordinate of ML = 4.2 mm. The caudorostral coordinate is shown above the map, and the depth coordinate is shown on the left. Inset: the best frequencies (BFs) of the stimulation sites in the auditory cortex. C and D: the responses of 2 neurons were sampled from 2 sites: 1 from the MGcm and the other from the MGv. They are shown in raster displays (C) and PSTHs (D). closed circles, the inhibitory effects of cortical activation on the thalamic neurons at the illustrated site; open circles, facilitatory effects; ×, no effect. For closed circles, the smaller ones indicate inhibitory effects between 20 and 50%, and the bigger ones those between 51 and 100%. For the open circles, the smaller ones indicate facilitatory effects between 20 and 100%, and the bigger ones those >100%. W, weak response to noise burst; N, no response to noise burst; L, response to noise burst with a latency longer than 50 ms; OFF, off response to auditory stimulus; ON-OFF, ON and OFF responses to auditory stimulus; Numbers in parentheses indicate the best frequency of the neuron in the recording site. These conventions apply to Figs. 6–8. Bar, 1 mm.
tory effects, 2 received no effects, and only 2 that were located near the border of MGv received inhibitory effects. The frontal plane shown in Fig. 6 was sampled at slightly caudally to the rostrocaudal midline of the MGB, which included the MGcm, MGv, and MGs. Activation of either the auditory field A or DC caused a mainly facilitatory effect on the neurons in the MGv, large inhibitory effects on the neurons in the MGcm, and smaller inhibitory effects on the neurons in the MGs. Electrical activation caused large inhibitory effects on the neurons in the MGcm, in contrast with the mainly facilitatory effects on the MGv neurons.

**Effects on the MGcm neurons**

Figure 7 shows a comparison of the corticofugal effects on neurons between the MGcm and MGv. In Fig. 7A, cortical activation at any of the indicated sites in either field A or DC induced mostly inhibitory effects on the neurons in the MGcm and mainly facilitatory effects, some no effect, and very few inhibitory effects on the MGv neurons. Figure 7B shows a relatively rostral section of the MGB, in which the MGcm and MGv can be distinguished based on the Nissl staining. An additional nucleus that responded to auditory stimulus was

![Diagram](image_url)
recognized as the posterior nucleus (Po) of the thalamus as defined previously (He 2001). Stimulation electrodes were all placed in cortical area A in this case. Of four neurons that were located in the MGrm, except for one neuron that showed no effect while site Z was activated, all showed inhibitory effects when the cortex was activated at any site. Activation of the cortex caused mixed modulatory effects on the neurons in the Po, mostly facilitatory and some inhibitory effects.

The inhibition on the MGrm caused through cortical activation was relatively weaker than that in the MGcm. In comparison with the 85% (174/204) of cases showing an inhibitory effect in the MGcm, 73% (62/84) of the cases showed an inhibitory effect in the MGrm. Samples that showed >50% inhibition occupied only 12% of the neurons in the MGrm, whereas this proportion in the MGcm was 36%.

Effects on the MGs neurons

In the example shown in Fig. 8, the recordings in MGs showed a strong inhibitory effect, whereas those in the MGv showed a facilitatory effect. As shown in Figs. 5 and 6, cortical activation mainly caused inhibitory effects in the MGs, although the inhibition magnitude was relatively weaker than that on the MGcm. On the MGs, 77% (83/108) of the samples showed inhibitory effects, but only 14% of the samples showed inhibitory effects of >50%.

Stimulation site specificity of the modulatory effect on the MGB

As shown in the statistics in the preceding text, most of the neurons in the nonlemniscal MGB were inhibited by the activation of any of the cortical sites in fields A and DC. The corticofugal inhibition of the nonlemniscal MGB was spread widely. No systematic difference in the modulatory effect could be detected between the different stimulation sites.

Corticofugal modulation on the off responses

As described earlier, off and on-off neurons count for 10–20% of the total MGB neurons. Most off and on-off neurons were located beyond/on the border of the lemniscal MGB (He 2001). The modulatory effect of cortical activation on the on responses could be either facilitatory or inhibitory, mainly depending on the location of the thalamic neurons. The modulatory effect on the nonlemniscal MGB was mainly inhibitory. However, of 54 off and on-off MGB neurons examined for the corticofugal modulatory effect on their off responses, 44 neurons showed a facilitatory effect (20–487%, mean ± SD: 111.4 ± 99.9%), 7 showed no effect, and 3 showed an inhibitory effect (19–29%, 25.7 ± 5.8%).

Off and on-off neurons that were located on the border region between the lemniscal and nonlemniscal nuclei and close to the lemniscal side were parceled into the border region (bMGv) of the MGv, and those that located nonlemniscal nuclei were correspondingly parceled into the MGcm, the MGrm, the MGs, and the MGd (He 2001, 2002). Of 54 off and on-off neurons examined, 30 were from the bMGv, 11 from the MGcm, 11 from the MGs, 1 from the MGrm, and 1 from the MGd. Because the numbers of neurons sampled from the MGrm and MGd were small, they were excluded from further analysis.

Off and on responses in the border region of the MGv.

The neuron in Fig. 9A, which was tuned to a BF of 12.5 kHz, showed facilitatory effects on the on response by 46, 79, and 33% with the cortical activation at sites X (field A, BF = 2 kHz), Y (15 kHz), and Z (18.5 kHz), respectively, while the off response was also facilitated by 24, 29, and 24% accordingly. Fourteen neurons showed facilitatory effects for both on and off responses, and were categorized as on-facilitated-off-facilitated (FF) neurons.

The neuron in Fig. 9B, which was located on the medioventral border of the MGv with the MGcm, was an on neuron when only a noise-burst stimulus was applied to the subject. The neuron, however, became an on-off neuron while any of the three cortical sites: X (field A, BF = 16 kHz), Y (field DC, BF = 21 kHz), and Z (field DC, between 14 and 17 kHz), was activated with electrical currents. The on responses of the neuron did not change significantly, but off responses appeared when the cortex was activated by any of the above sites. The neuron was classified as an on-unknown-off-facilitated (UF) neuron.

On-off neurons located on the border between the lemniscal and nonlemniscal MGB, but near the lemniscal MGB side, showed a facilitatory effect on their off responses by cortical activation, as in another example shown in Fig. 9C. The on-off neuron in Fig. 9C, which was located in the dorsal border of the MGv, showed a great increase in the on response only when site Y (field A, BF = 7 kHz) was activated. However, the off response was not affected by any of the cortical activation. This neuron was classified as on-facilitated-off-unknown (FU) type. The neuron had single-peaked tuning curves for both on and off responses, with a BF of ~20 kHz.

Off and on responses in MGcm.

Both on-off neurons, which were located in the MGcm, in Fig. 10A and B, decreased their on responses and increased their off responses when the auditory cortex was activated. The neuron in Fig. 10A decreased its on response by 44, 31, and 19% and increased its off response by 71, 75, and 110% when the cortical sites, X (field A, BF = 2.8 kHz), Y (12.5 kHz), and Z (16 kHz), respectively, were activated. The neuron in Fig. 10B showed a strong on response and a weak off response, in the control condition (E-). The on response was almost switched off by any of the EX, EY, and EZ (same as Fig. 10A). However, the off response was greatly increased, by 257, 128, and 300%, whereas one of
the above sites was activated accordingly. Nineteen ON–OFF neurons were grouped in the same category as the neurons in Fig. 10, namely, ON–inhibited–OFF–facilitated (IF) neurons. On average, the ON responses decreased by 47.0 ± 21.1% (20–82%), and the OFF responses increased by 120.1 ± 114.5% (20–487%), while the most effective site for ON responses among the three electrodes was activated for each of these neurons.

The neuron in Fig. 10C showed a burst-like ON response and an OFF response consisting of a singular spike and a burst-like rebound. The ON response, which had a long latency of 36 ms, was completely suppressed by the electrical stimulation at either site X (field A, BF = 2.8 kHz) or site Y (12.5 kHz) but unaffected by the stimulation at site Z (16 kHz). However, the OFF response including the singular-spike and the rebound was not affected by the cortical activation as shown in the spike counts. This neuron was classified as ON–inhibited–OFF–unknown (IU) type. The location of the neuron was anatomically confirmed in the MGcm of the nonlemniscal MGB.

OFF RESPONSES IN MGs. The neuron shown in Fig. 11 was an OFF neuron, and responded to noise bursts and increased its firing rate by ~60% while the cortical field A (BF = 7 kHz) was activated with 100 μA and by ~67% with 200 μA (Fig. 11, A and B). The neuron showed a double-peak frequency tuning of 12.5 and 16.5 kHz in its rate-frequency functions at 30 and 40 dB SPL (Fig. 11C) and was located in the MGs. The OFF neuron was confirmed as its response after the offset of the stimulus as we prolonged the stimulus-duration from 200 (Fig. 11A) to 400 ms (Fig. 11C, inset).

Pure OFF neurons only counted for 12% (7 over 56) of the OFF and ON–OFF neurons. Six of them showed corticofugal facilitatory effects, whereas one showed no effect.

Location dependence of modulatory effects on OFF response

Neurons located on the bMGv showed the greatest variety: 12 FF, 4 FU, 2 on-facilitated-off–inhibited (FI), 6 UF, 4 IF, and 2 IU neurons. Of 11 neurons located in the MGs, 5 were UF,
The neurons in the MGcm were the most homogeneous: 10 IF and 1 IU. More than half of the ON-OFF neurons (18/30) on the bMGv showed facilitatory corticofugal effects, only a small portion (6/30) showed inhibitory effects, and the remaining six showed no effect on their ON responses, whereas the corticofugal modulatory effects on their OFF responses were even more facilitatory (22/30) with only two neurons showing an inhibitory effect.

The majority of the neurons in the MGs showed either UF (5/11) or IF (4/11) type, indicating that their ON responses were either unaffected or inhibited by the corticofugal modulation, whereas their OFF responses were facilitated by the corticofugal modulation.

All neurons in the MGcm showed inhibitory effects on the ON response by the corticofugal modulation. However, apart from one neuron that showed no effect, all the other neurons showed facilitatory effects on the OFF response by corticofugal modulation.

Summary of the facilitatory and inhibitory effects on the ON and OFF responses in the bMGv, MGs, and MGcm is shown in Fig. 12. ON responses of the ON-OFF neurons in the bMGv were mainly facilitated by the corticofugal modulation, whereas those in the MGs and MGcm were mainly inhibited. However, the OFF responses in all divisions were mainly facilitated by the corticofugal modulation.

**DISCUSSION**

**Methodological consideration**

Comparing with our results, earlier studies using cooling technique to inactivate the already suppressed anesthetized cortex showed relatively smaller corticofugal effects on fewer MGB neurons than the present and previous studies using cortical activation methods (He 1997; He et al. 2002; Jen et al. 1998; Ryugo and Weinberger 1976; Suga et al. 1997; Sun et al. 1989; Villa et al. 1991).

With a train of 0.1-ms pulses in most of the cases, we found that the current threshold to evoke a corticofugal modulatory effect on the auditory thalamus was between 50 and 100 μA for guinea pig neurons. The current used in the electrical stimulation of the cortex and the thalamus of the in vivo subject varied from 100 nA (Chowdhury and Suga 2000; Ma and Suga 2001a,b; Sakai and Suga 2001; Suga et al. 2000; Xiao and Suga 2002; Yan and Suga 1996, 1998; Zhang and Suga 2000; Zhang et al. 1997) to hundreds of microamperes or even 10 mA among different investigators [5–50 μA.
consumption and delineates regions of activity, Gonzalez-Lima and Scheich (1984) quantitatively showed that a region of ~1 mm in diameter was activated with 0.2-ms pulse trains of 300–600 μA; this is equivalent to 0.1-ms pulse trains of 600–1,200 μA in energy. It is predicted that 100–200 μA would activate a region of ~0.5 mm in diameter or smaller (Banck 1975). We recommend a careful calibration for experiments using 100 nA as the stimulation current (Xiao and Suga 2002; Yan and Suga 1996, 1998; Zhang et al. 1997; see also discussion in He et al. 2002).

The effective time interval between the electrical stimulation and the acoustic stimulus peaked at 50–150 ms and lasted for >300 ms (Fig. 4) (also see He et al. 2002).

**Corticofugal modulation as a gain controller**

Previous studies have indicated that nonspecific cortical stimulation (stimulation site functionally mismatched with the recording site in the IC) overwhelmingly resulted in suppressive effects, whereas matched sites could result in facilitation (Gao and Suga 1998; Zhang and Suga 1997; Zhang et al. 1997; Zhou and Jen 2000). Using cortical inactivation method of muscimol application, Zhang and Suga (1997) found that the corticofugal system amplifies collicular auditory responses by 1.5 times and thalamic responses by 2.5 times on average. Although the majority of the corticofugal fibers go to the thalamus, a fraction project to the pericentral nucleus (ICx) of the IC, and each projection extends to a broad region in the ICx (Budinger et al. 2000; Saldaña et al. 1996). It was confirmed that the projection from the ICx to the central nucleus could be inhibitory (Jen et al. 2001).

A similar phenomenon has also been observed in the cat MGv, where the interneurons count for a fourth of the total population (He et al. 1997; Villa et al. 1991). However, the inhibitory effect became very minor on the MGv of the guinea pig and the bat, where the interneurons count for only 1% of the population (see He et al. 2002; Yan and Suga 1999).

![FIG. 11. Modulatory effects of cortical activation on an OFF neuron in the MGs. A: raster displays show the neuronal responses to noise-burst stimuli, in the control condition (E-) and while the cortex was activated at field A (BF = 7 kHz) in various currents: 100 and 200 μA. Noise bursts of 200-ms duration and 60 dB SPL were repeated at 1-s interstimulus-intervals. B: bar graph shows the spike counts of OFF responses in various conditions. Spike counts were made for 100 ms after the onset of the stimulus. C: rate-frequency functions in 3 SPLs show the frequency tuning of the OFF response. Insets: the PSTHs of 2 sampling points from the functions.

![FIG. 12. Spatial distributions of various types of OFF and ON-OFF corticofugal-modulatory neurons. Only those neurons located in the bMGv, MGs, and MGcm were counted in the statistics. Those neurons whose ON and OFF responses were not affected by the cortical stimulation of the implanted electrodes were not counted in the statistics and were regarded as their effects unknown. Facilitatory and inhibitory effects on the ON and OFF responses were separately counted for each of the preceding 3 subdivisions.]
Strong corticofugal inhibitory effect on the nonlemniscal MGB

In contrast to the strong facilitatory effect on the lemniscal nucleus (Figs. 5B and 6) (He 1997; He et al. 2002; Suga et al. 1997, Fig. 4; Villa et al. 1991; Yan and Suga 1999; Zhang and Suga 1997), we observed a mostly inhibitory effect on the ON responses of the nonlemniscal MGB neurons after cortical activation. Watanabe et al. (1966) obtained corticofugal modulatory effects from only 20 of 292 MGB neurons. Of these, 6 showed a facilitatory effect and 14 were strongly inhibited by cortical activation. Referring to their data (Watanabe et al. 1966, Fig. 4), the illustrated neuron was an ON-OFF neuron, which is very often found in the nonlemniscal MGB or on the border of the lemniscal and nonlemniscal MGB (He 2001), and was a burst-firing neuron, which was more likely to be a nonlemniscal neuron (He and He 2002). Therefore it would be reasonable to speculate that a great proportion of the inhibitory effect neurons reported by Watanabe et al. (1966) were sampled from the nonlemniscal nuclei of the MGB. Villa et al. (1991) observed more neurons in the medial division of the MGB showing increased spontaneous firing rate than other subdivisions when the auditory cortex was cooled.

The inhibitory effect on the nonlemniscal MGB was generally widespread as we observed inhibitory effects from all three cortical stimulation sites in many cases, although there were exceptional cases in which only one or two sites showed inhibitory effects. Under the present anesthetized condition, we observed a relatively lower spontaneous firing of the thalamic neurons comparing with those in the cortical and thalamic neurons in lightly anesthetized animals (Edeline et al. 2000, 2001; Zurita et al. 1994). It is worth of mention that the observations may be limited to excitatory components, and, if inhibition components would have been detected, the proportion of corticofugal facilitatory effects on the nonlemniscal MGB might have been slightly larger.

Mechanism of the corticofugal inhibition on the nonlemniscal MGB

Morphologically the GABAergic terminals form synapses on every part of the relay neurons with a higher portion at the proximal and intermediate parts of the neuron than the distal parts (Liu et al. 1995a). However, the corticothalamic terminals have their main contacts on the distal dendrites having an accumulative effect, which could be overcounterbalanced by the strong GABAergic inhibition (Golshani et al. 2001). Although the thalamocortical and corticothalamic pathways are roughly reciprocally connected (Andersen et al. 1980; Berson and Graybiel 1983; Merzenich et al. 1982), there are some discontinuities between them (Winer and Larue 1987). In a previous study, we found fewer corticofugal direct projections to the nonlemniscal MGB than to the lemniscal MGB (He and Hashikawa 1998).

There are three possible pathways to inhibit the nonlemniscal MGB.

VIA THALAMIC INTERNEURONS. Recent anatomical studies have revealed that there are very few interneurons in the rodent MGB: <1% in the guinea pig and rat (Arcelli et al. 1997; Winer and Larue 1996). Therefore the pathway through the thalamic interneurons is excluded from the candidates for the strong corticofugal inhibitory pathway. Another possible inhibition is from the presynaptic dendrites (PSDs) of the interneurons on the thalamic relay neurons (He 1997; Liu et al. 1995a; Pinault and Deschênes 1998; Raston et al. 1988). However, the PSDs count for only <6% of the total terminals, compared with an average of 35% inhibitory terminals on the cat thalamus where interneurons counts for 24–27% of the total population (Liu et al. 1995a; Rinvik et al. 1987). With a few interneurons in the guinea pig thalamus, it is unlikely that the strong and nucleus-specific inhibition is mainly caused by the PSDs.

VIA IC GABAERGIC NEURONS. The auditory cortex projects to the IC and the projections are excitatory (Herbert et al. 1991; Ojima 1994; Winer et al. 1998). In the cat, ~20% of the neurons in the central nucleus of the IC are GABAergic (Olive et al. 1994). Among the tectothalamic projection IC neurons, GABAergic neurons count for 14–36% in the cat and 20–45% in the rat (Peruzzi et al. 1997; Winer et al. 1996). In a recent in vivo intracellular recording, we could still record a strong, long-lasting inhibition in the MGB after an electrical stimulation of the auditory cortex with a pulse train after the section of the tectothalamic fibers, suggesting that the strong inhibition was not via the IC pathway (Fujimoto et al. 2002).

Some recent results from studies on bats hint that the corticocollicular projection might be more involved in experience-dependent plasticity (Gao and Suga 1998, 2000; Jen et al. 1998; Ji et al. 2001; Suga et al. 2000; Yan and Suga 1998; Zhang et al. 1997; Zhou and Jen 2000).

VIA RTN NEURONS. The majority of the excitatory inputs to the RTN neurons are derived from the cerebral cortex (Liu and Jones 1999), indicating that the corticofugal fibers to the RTN neurons control the RTN neurons’ excitability. The RTN neurons extend dendrites within the thin reticular sheet, which enable them to receive projections from a wide cortical region and project to widespread areas in the ventroposterior nucleus of the thalamus (Liu et al. 1995b). This, together with the results of other studies, leads to the reasonable conclusion that the control of the thalamus via the RTN is widespread (Bourassa et al. 1995; Cox et al. 1997; Liu et al. 1995b; Ohara et al. 1980).

Giants GABAergic terminals have been found only in the nonlemniscal nuclei of the MGB and not in the MGv of the cat (Winer et al. 1999). Compared with the labeling of the giant GABAergic terminals in the cat MGB (Winer et al. 1999, Fig. 3), the agreement of the map with the inhibitory corticofugal modulation on the guinea pig MGB is surprising, especially the region with strong inhibition of >50% in the present report (Fig. 5).

Recent morphological and physiological results indicate that the RTN terminals have a very strong inhibitory effect on the thalamic relay neurons (Bartlett et al. 2000; Golshani et al. 2001). In summary, activation of the cortex directly generates excitatory input to the MGB neurons including nonlemniscal neurons on the one hand and also activates the RTN neurons through corticothalamic fibers on the other hand, which in turn inhibits the nonlemniscal neurons. This might be the reason why we observed in some cases only one or two sites of three implanted stimulation electrodes showing inhibitory effects on the thalamic neurons while the remainders showed no effect or even facilitatory effect.

A cortical stimulation with a small current on any of the three stimulation sites showed a similar inhibitory effect as
shown in Figs. 3B and 6. A stronger stimulation current caused
a stronger inhibition on the nonlemniscal MGB neurons. These
results might be explained by the widely stretched dendrites
and terminal fields of the KT neurons (Bourassa and Des-
chènes 1995; Jones 1975; Pinault et al. 1997; Shosaku and

Corticofugal modulation on OFF responses

The present results reveal that the corticofugal modulation
on the OFF response showed mainly facilitatory effects. For
ON responses of the ON-OFF neurons in the bMGv were mainly
facilitated by the corticofugal modulation, whereas those in
the MGs and MGcm were mainly inhibited. A result in an early
report by Villa et al. (1991, their Fig. 6C), that an inactivation
of the cortex caused an increase in the ON response and a
decrease in the OFF response of a cat MGm neuron, agreed with
the present results very well. It is reasonable to conclude that
the OFF response is produced as the disinhibition from the
inhibitory input of the auditory stimulus. One of our recent
intracellular studies showed that OFF responses had happened in
many cases in hyperpolarized neurons with a low-threshold
calcium spike/spike train (Yu et al. 2002a). A further hyper-
polarization caused by the cortical stimulation makes a stron-
ger disinhibition on the OFF response, causing an increase in
the spike number.

Differential corticofugal projections from layers V and VI

Previous anatomical results have shown that the layer VI
neurons in the primary auditory field project mainly to the
lemniscal MGB with small boutons and the layer V neurons
project to the nonlemniscal MGB and IC with giant boutons
(Bajo et al. 1995; Ojima 1994; Winer et al. 1999; see Bourassa
et al. 1995 for somatosensory system). In the present study, we
inserted the stimulation electrodes into 1,000 μm deep of the
cortex and used an average of 100–300 μA current, which
would most probably spread into both layers. The corticofugal
facilitatory effect on the MGv as observed in the previous and
present studies is likely to be caused by the small-size boutons
that terminate mainly in the distal part of the dendrite and
supposedly cause a long time-constant effect on the relay
neurons (He 1997; He et al. 2002; Liu et al. 1995a, McCormick
and von Krosigk 1992; Winer et al. 1999). The relationship
between the giant corticothalamic boutons in the nonlemniscal
MGB and the corticofugal modulation is to be investigated by
a comparison between selective activations of the layer V and
the layer VI using small electrical current (<100 μA). The
nonlemniscal MGB neurons show a burst-firing mode much
more often than lemniscal MGB neurons (He and Hu 2002)
and also show an oscillation mode, which is never observed in
the core region of the MGv in the anesthetized animal (unpub-
lished observation). In vivo intracellular recording showed that
a thalamic neuron has several firing modes (Yu et al. 2002b).
The giant boutons might be involved in the controlling of the
firing mode of the nonlemniscal neurons.

Functional implication of the inhibitory effect on MGcm

The MGcm, which is equivalent to the magnocellular divi-
sion of the MGB in the cat and monkey, consists of large and
deeply Nissl-stained cells and projects to the entire auditory
cortex (Redies and Brandner 1991), hinting at a power to adjust
the total activity of the auditory cortex. The MGcm is involved in
the integration of multi-sensory afferents (Edeline 1990;
Edeline and Weinberger 1992; Wepsic 1966; Winer and Mo-
rest 1983). The present results, showing that the activated
primary auditory cortex strongly inhibited the MGcm while
strongly facilitating the MGv, provide a possible explanation
for the selective gating of the auditory information through the
lemniscal MGB while switching off other unwanted sensory
signals and the interference from the limbic system, leaving
the auditory cortex prepared to process only the auditory signal.

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REFERENCES

Amato G, La Grutta V, and Enia F. The control exerted by the auditory
cortex on the activity of the medial geniculate body and inferior colliculus.

Andersen RA, Knight PL, and Merzenich MM. The thalamocortical and
corticothalamic connections of AL AII, and the anterior auditory field
(AAF) in the cat: evidence for two largely segregated systems of con-

Arcelli P, Frassoni C, Regondi MC, De Biasi S, and Spreat e Ros. GABAer-
gic neurons in mammalian thalamus: a marker of thalamic complexity?

Bajo VM, Rouiller EM, Welker E, Clerke S, Villa AEP, de Ribau pierry Y,
and de Ribau pierry F. Morphology and spatial distribution of corticotha-
lamic terminals originating from cat auditory cortex. Hear Res 83: 161–174,
1995.

Banck JB Jr. Which elements are excited in electrical stimulation of mam-

Bartlett EL, Stark JM, Guillery RW, and Smith PF. Comparison of the fine
structure of cortical and collicular terminals in the rat medial geniculate

Berson DM and Graybiel AM. Organization of the striate-recipient zone
of the cat’s lateralis posterior-pulvinar complex and its relations with the

Bourassa J and Desch ˆenes M. Corticothalamic projections from the primary
visual cortex in rats: a single fiber study using biocytin as an anterograde

Bourassa J, Pinault D, and Desch ˆenes M. Corticothalamic projections from
the cortical barrel field to the somatosensory thalamus in rats: a single-fibre
study using biocytin as an anterograde tracer. Eur J Neurosci 7: 19–30,
1995.

cortex in the Mongolian gerbil (Meriones unguiculatus). IV. Connections
with anatomically characterized subcortical structures. Eur J Neurosci 12:

Calford MB and Aitkin LM. Ascending projections to the medial geniculate
body of the cat: evidence for multiple, parallel auditory pathways through

Chowdhury SA and Suga N. Reorganization of the frequency map of the
auditory cortex evoked by cortical electrical stimulation in the big brown

Chung S and Suga N. Functional reorganization of the cortex of cats

Crick F. Function of the thalamic reticular nucleus: the searchlight hypothesis.

Cruikshank SJ, Edeline JM, and Weinberger NM. Stimulation at a site of
auditory-somatosensory convergence in the medial geniculate nucleus is an
effectively unconditioned stimulus for fear conditioning. Behav Neurosci 106:


