Specific and Nonspecific Plasticity of the Primary Auditory Cortex Elicited by Thalamic Auditory Neurons

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The ventral and medial divisions of the medial geniculate body (MGBv and MGBm) respectively are the lemniscal and nonlemniscal thalamic auditory nuclei. Lemniscal neurons are narrowly frequency tuned and provide highly specific frequency information to the primary auditory cortex (AI), whereas nonlemniscal neurons are broadly frequency tuned and project widely to auditory cortical areas including AI. The MGBv and MGBm are presumably different not only in auditory signal processing, but also in eliciting cortical plastic changes. We electrically stimulated MGBv or MGBm neurons and found the following: (1) electric stimulation of narrowly frequency-tuned MGBv neurons evoked the shift of the frequency-tuning curves of AI neurons toward the tuning curves of the stimulated MGBv neurons. This shift was the same as that in the central nucleus of the inferior colliculus and AI elicited by focal electric stimulation of AI or auditory fear conditioning. The widths of the tuning curves of the AI neurons stayed the same or slightly increased. (2) Electric stimulation of broad frequency-tuned MGBm neurons augmented the auditory responses of AI neurons and broadened their frequency-tuning curves which did not shift. These cortical changes evoked by MGBv or MGBm neurons slowly disappeared over 45–60 min after the onset of the electric stimulation. Our findings indicate that lemniscal and nonlemniscal nuclei are indeed different in eliciting cortical plastic changes: the MGBv evokes tone-specific plasticity in AI for adjusting auditory signal processing in the frequency domain, whereas the MGBm evokes nonspecific plasticity in AI for increasing the sensitivity of cortical neurons.

Introduction

The medial geniculate body (MGB) that relays auditory signals from the inferior colliculus (IC) to the auditory cortex (AC) consists of the ventral division (MGBv) of the lemniscal pathway and the medial (MGBm) and dorsal (MGBd) divisions and the posterior intralaminar nucleus (PIN) of the nonlemniscal pathway (Imig and Morel, 1983). The lemniscal pathway is tonotopically organized (Aitkin and Webster, 1972; Clarey et al., 1992), whereas the nonlemniscal pathway is not tonotopically organized and is multisensory (Calford and Webster, 1981; Calford, 1983; Winer and Morest, 1983; Imig and Morel, 1988). Lemniscal neurons are narrowly tuned to a specific single frequency and respond to repetitive tonal stimuli in fidelity. In contrast, nonlemniscal neurons are broadly frequency tuned and rapidly adapt to repetitive identical stimuli (Aitkin and Webster, 1972; Phillips and Irvine, 1979). Lemniscal neurons project to the middle layers of the primary auditory cortex (AI), whereas nonlemniscal neurons broadly project to the superficial layers of the auditory cortical areas including AI (Jones, 1985; Winer, 1992). Different from lemniscal thalamic neurons, nonlemniscal thalamic neurons project to the limbic system such as the amygdala, insular–temporal lobe, and striatum (Shinonaga et al., 1994; Deschênes et al., 1998; Doron and Ledoux, 2000). These anatomical and physiological differences between the lemniscal and nonlemniscal neurons indicate

that they engage in different aspects of auditory signal processing (Aitkin and Prain, 1974; Calford and Aitkin, 1983; Lennartz and Weinberger, 1992) and also in evoking different types of plastic changes (Suga, 2008).

When auditory fear conditioning with a pair of a conditioning tone stimulus (CS) and an unconditioned electric leg or foot stimulus (US) is delivered to an animal such as the guinea pig (for review, see Weinberger, 1998) or big brown bat (for review, see Suga et al., 2002), AI and subcortical auditory neurons shift their frequency tuning curves or receptive fields. That is, they show a best frequency (BF) shift. When the CS and US are unpaired for pseudoconditioning, however, AI and subcortical neurons show nonspecific augmentation (sensitization). How do the lemniscal and nonlemniscal pathways play a role in evoking these two types of cortical plastic changes which are incompatible to each other. Weinberger (1998) hypothesized that the MGBm/PIN evokes the small cortical BF shift, whereas Gao and Suga hypothesized that the MGBv evokes it. Then Suga (2008) further hypothesized that the MGBv evokes the small cortical BF shift whereas the MGBm evokes a small cortical nonspecific augmentation. One of the critical experiments to test these hypotheses is to examine the effect of electric stimulation of narrowly frequency-tuned MGBv neurons or broadly frequency-tuned MGBm neurons on AI neurons. Therefore, we studied changes in AI neurons elicited by electric stimulation of MGBv and MGBm neurons, and found that the MGBv neurons evoked cortical BF shifts, but MGBm neurons did not. Instead, they evoked nonspecific augmentation.

Materials and Methods

Materials, surgery, acoustic stimulation, electric stimulation, recording of action potentials, and data acquisition and processing were basically

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Figure 1. Electrode assembly and recorded/stimulated sites. **A**, An electrode assembly used for recording of action potentials and electric stimulation. **B**, A coronal section across the medial geniculate body, MGB (Nissl stain, 60 μ m thick). MGBm, The medial division of the MGB. MGBv, The ventral division of the MGB. 1 and 2, Electrode penetrations across the hippocampus (HPC) and MGBv or MGBm.

the same as those described by Ma and Suga (2001a, 2007), although the site of electric stimulation was the MGB instead of AI. Therefore, only the essential portions of the methods are described below.

Eleven adult big brown bats (*Eptesicus fuscus*) were used for the current experiments. Under neuroleptanalgesia (Innovar 4.08 mg/kg b. w.), a 1.5-cm-long metal post was glued on the dorsal surface of the bat's skull. Physiological experiments were started 3–4 d after the surgery. The awake animal was placed in a polyethylene-foam body mold that was hung with an elastic band at the center of a soundproof room maintained at $\sim 31^\circ\text{C}$. The metal post glued on the skull was fixed to a metal rod with set screws to immobilize the animal's head, and the head was adjusted to face directly toward a loudspeaker located 74 cm away. Holes (~ 500 μ m in diameter) were made in the skull covering the auditory cortex (AC). Through the hole, a multi-electrode assembly (Fig. 1A) (NeuroNexus Technologies) was inserted into AI for recording the auditory response (action potentials) of an AI neuron and for studying its frequency tuning. An electrode of the assembly which did not record any auditory responses was used as a reference electrode. Through another hole, another multi-electrode assembly was dorsoventrally inserted in a coronal plane into the MGB through the posterior part of AI and the hippocampus for recording auditory responses (action potentials) of MGB neurons (Fig. 1B), so that we first observed the responses of cortical auditory neurons, regular spontaneous discharges of hippocampal neurons and then the auditory responses of MGB neurons. The electrode which did not record any auditory responses on the same pin was selected as a reference electrode. After recording and studying the auditory responses of MGB neurons, these electrodes were connected to the cathode and anode of the constant current stimulus isolator for electric stimulation. The distance between two electrodes was vertically 50–150 μ m. Because of this vertical short distance, the stimulation was limited in a nucleus. The effect of the electric stimulation on the frequency tuning of the AI neuron was then studied. The protocol for this research was approved by the Animal Studies Committee of Washington University in St. Louis.

Acoustic stimulation. For the measurement of the frequency-threshold (tuning) or -response curve and the best frequency (BF) of a MGB and an AI neuron, a 4.0 ms tone burst, including a 0.5 ms rise–decay time, was delivered to the animal from a leaf tweeter (Panasonic, model EAS-10 TH-800) at a rate of 5/s. Its frequency and amplitude were varied manually or computer-controlled (TDT System 3, Tucker-Davis Technolo-

gies). Before the experiments, the sound amplitude was calibrated with a Brüel & Kjær 1/4 inch calibrated microphone (model 4135) placed at the location of the bat's head and was expressed in decibels in sound pressure level (dB SPL) referencing 20 Pa root-mean-square.

The frequency-tuning curve of a MGB or an AI neuron was first audiovisually measured. Then, the tone burst was randomly changed in amplitude in 5 dB steps from 0 to 100 dB SPL and in frequency in 0.5 kHz steps between -5.0 and 5.0 kHz of the BF if the tuning curve was narrow, but in 1.0 kHz steps between -10 and 10 kHz of the BF if it was broad, by TDT System 3 (Tucker-Davis Technologies). This frequency-amplitude scan was repeated five times to obtain five responses at each frequency-amplitude combination. It took 7 min to complete the five scans. A frequency-tuning curve of a neuron was obtained from its responses to the frequency-amplitude scans. The frequency-response curve of the neuron was obtained by counting the number of action potentials at 30 dB above the minimum threshold of the neuron as a function of frequency.

Action potentials of AI and MGB neurons. AI neurons were recorded at depths between 300 and 700 μ m from the cortical surface, whereas MGB neurons were recorded at depths between 2700 and 3300 μ m from the cortical surface.

We used an amplitude-window discriminator software (Tucker-Davis Technologies) to select action potentials of a single neuron. At the beginning of data acquisition, the waveform of an action potential was stored and displayed on the monitor screen. The data acquisition was continued as long as other action potentials obtained during data acquisition matched with this action potential (i.e., template).

Electric stimulation. An electric stimulator (Grass, S88) and a constant current isolator (WPI, A360) were used for focal electric stimulation of the MGB. A 6.2 ms train of four monophasic electric pulses (100 nA constant current, 0.2 ms duration, 2.0 ms interval) was delivered to MGB neurons at a rate of 10/s for 30 min through two electrodes of the electrode assembly as described above. The bat showed no behavioral response at all to such weak electric stimulation. At the end of the last neurophysiological experiment on an animal, a 10-s-long, 500 nA monophasic electric current was applied to the stimulation electrodes to make a lesion at the stimulated site (Fig. 1B).

Data acquisition and processing. Data obtained before and after the focal electric stimulation of the MGB were stored on a computer hard drive and were used for off-line data processing that included plotting frequency-tuning and -response curves and measuring the BF, MT, and Q-value at 30 dB above the minimum threshold of a given neuron. The paired *t* test was used to test the difference between the responses obtained before and after the electric stimulation.

The frequency-threshold curves of the thalamic neurons could be easily classified into either sharply tuned or multi-peaked broadly tuned. However, they should be defined with the quality factors of the curves. So, we calculated a Q-30 dB value (a BF divided by the threshold curve width at 30 dB above the minimum threshold of a given neuron) instead of a Q-10 dB value, because the Q-10 dB value in a multi-peaked tuning curve was large and did not appropriately represent the sharpness of the curve. For each frequency-threshold curve, we defined the broadly tuned neuron when its Q-30 dB was <6.0 and the sharply tuned neuron when its Q-30 dB was larger than 9.0. Neurons with a Q-30 dB between 6.0 and 9.0 were classified as intermediately tuned.

Results

The electrode assembly (Fig. 1A) was placed 1.3–2.3 mm lateral to the midline and was inserted dorsoventrally into the MGB

through the posterior portion of AI and the hippocampus (Fig. 1*B*). Auditory responses of MGB neurons were recorded below hippocampal neurons which showed regular spontaneous discharges.

The BFs of the cortical neurons studied ranged from 19 to 56 kHz (33.1 ± 6.35 kHz), and the BFs of the MGB neurons studied range from 15 to 55 kHz (31.4 ± 6.7 kHz).

Figure 2 displays the receptive fields of two thalamic (*A1* and *B1*) and two cortical (*A2–A4* and *B2–B4*) neurons based upon the responses to the frequency-amplitude scans repeated five times. The thalamic neuron in *A1* was sharply tuned to 32.0 kHz, whereas that in *B1* was broadly tuned to multiple frequencies. Its BF was 25.0 and/or 28.0 kHz. On the other hand, the cortical neurons both were sharply tuned to 29.0 (*A2*) or 26.0 (*B2*) kHz. When the sharply tuned thalamic neuron (*A1*) was electrically stimulated, the frequency-tuning curve (or receptive field) of the cortical neuron sharply tuned to 29.0 kHz (*A2*) shifted its frequency-tuning curve toward that of the stimulated neuron, so that the BF of this cortical neuron shifted from 29.0 kHz to 30.0 kHz. The width of the tuning curve of the cortical neuron slightly widened (*A3*), so its Q-30 dB changed from 10.6 to 9.7. The shifted BF returned to the control BF ~60 min after the onset of the electric stimulation (*A4*). The BF shift or tuning shift was generally based on a decrease in response (inhibition) at the BF of the cortical neuron in the control condition and an increase in response (facilitation) at the BF of the stimulated thalamic neuron. Such a BF shift is also elicited by auditory fear conditioning, and has been known as a “tone-specific plastic change” (for review, see Suga and Ma, 2003).

When the broadly tuned thalamic neuron (Fig. 2*B1*) was electrically stimulated, the responses of the cortical neuron sharply tuned to 26.0 kHz (*B2*) were augmented to tone bursts from 18 to 37 kHz, so its receptive field was broadened, changing its Q-30 dB from 13.5 to 5.4 (*B3*). The BF of the cortical neuron did not shift. This augmentation almost disappeared 60 min after the onset of the electric stimulation (*B4*). Such augmentation of the responses of cortical neurons occurred over many frequencies even for electric stimulation of the thalamic neurons whose BF was 26 kHz different from the cortical neurons. Therefore, the augmentation was nonspecific to the BF of the stimulated thalamic neurons. That is, the cortical changes evoked by the broadly tuned thalamic neurons were “nonspecific plastic changes.”

The cortical BF shift and nonspecific augmentation evoked by thalamic stimulation are further documented with the frequency-threshold (tuning) and -response curves obtained from cortical neurons different from those shown in Figure 2. In Figure 3*A1*, the frequency-threshold curve of a thalamic neuron was sharply tuned to 31.0 kHz. When this neuron was electrically stimulated, the BF of the sharply tuned cortical neuron (*A2*, open

Figure 2. Changes in the receptive fields of two neurons in the primary auditory cortex (AI) evoked by electric stimulation of sharply tuned or broadly tuned neurons in the medial geniculate body (MGB). *A1, B1*, The receptive fields of the sharply tuned and broadly tuned MGB neurons, respectively. *A2, B2*, The receptive fields of AI neurons in the control condition. *A3, A4*, The receptive fields of AI neurons changed by electric stimulation of the MGB neurons shown in *A1* and *B1*, respectively. The change was either a best frequency (BF) shift (*A3*) or broadening of the receptive field (*B3*) depending on whether the stimulated neurons were sharply tuned or broadly tuned. *A4, B4*, Recovery of the receptive fields. Each black dot represents the number of action potentials discharged by the single neuron to five identical stimuli. See the scale at the lower right.

circles) shifted from 33.0 kHz to 32.0 kHz (*A2*, filled circles). That is, the BF shifted toward the BF of the stimulated thalamic neuron. The shape of the curve changed little. The shifted BF reverted to the control BF 60 min after the onset of the electric stimulation (*A2*, dashed line). In Figure 3, *B1* and *B2*, respectively, show the frequency-response curves of these thalamic and cortical neurons obtained at 30 dB above their minimum thresholds. The frequency-response curves of these neurons were sharply tuned to 31.0 and 33.0 kHz, respectively. Electric stimulation of the thalamic neuron evoked a 1.0 kHz shift of the BF of the cortical neuron toward the BF of the stimulated thalamic neuron. The width of the curve changed little (*B2*, filled circles). The change disappeared ~60 min after the onset of the electric stimulation (*B2*, dashed line). From these frequency-threshold and -response curves, it was clear that the sharply tuned thalamic neuron evoked the BF shift of the cortical neuron with little change in the shape of its tuning curves.

Figure 4, *A1* and *B1*, shows the broad frequency-threshold and -response curves of a thalamic neuron, respectively. Its BF was 25.0 kHz. Electric stimulation of this neuron evoked nonspecific augmentation of a cortical neuron tuned to 28.5 kHz (Fig. 4*A2, B2*, open circles). That is, the frequency-threshold and

Figure 3. Changes in the frequency-threshold (**A**) and frequency-response (**B**) curves of an AI neuron evoked by electric stimulation of a sharply tuned MGB neuron. Electric stimulation of the MGB neuron (**A1**, **B1**) evoked a shift of the frequency-threshold (**A2**) and frequency-response (**B2**) curves of the AI neuron. The open and filled circles represent the curves in the control condition and 30 min after the onset of the electric stimulation, respectively. The dashed lines represent the curves obtained 60 min after the onset of the electric stimulation. The frequency-response curves were measured at 30 dB above the minimum threshold of the given neuron.

Figure 4. Changes in the frequency-threshold (**A**) or frequency-response (**B**) curves of an AI neuron evoked by electric stimulation of a broadly tuned MGB neuron. The electric stimulation of the MGB neuron (**A1**, **B1**) evoked broadening of the frequency-threshold (**A2**) and frequency-response (**B2**) curves of the AI neuron. See Figure 3 legend for the symbols.

-response curves of the cortical neuron became broader (**A2** and **B2**, filled circles). A percentage increase in response was small at the BF but large at frequencies away from the BF. In the control condition, this cortical neuron did not respond to tone bursts <22 kHz and >32 kHz at 30 dB SPL, but responded to those <22 kHz and >32 kHz. The BF did not shift. The broadened curves reverted to the control condition ~60 min after the onset of the electric stimulation (**A2** and **B2**, dashed lines). From the changes in these curves, it was clear that, different from the sharply tuned

thalamic neuron, the broadly tuned thalamic neuron evoked nonspecific augmentation of the cortical neuron.

In Figure 5, **A** and **C**, shows the distributions of Q-30 dB values of the 45 stimulated thalamic and 66 recorded cortical neurons. Among the thalamic neurons, 15 had a Q-30 dB smaller than 6.0. Their Q-30 dB values ranged between 2.0 and 6.0 (3.2 ± 1.28). They were broadly tuned and multi-peaked. Their BFs (center frequencies of multi-peaked broad threshold curves) ranged from 19 to 55 kHz ($m \pm SD$: 33 ± 3.8 kHz). Twenty-six thalamic neurons studied had a Q-30 dB larger than 9.0. Their Q-30 dB values ranged between 9.5 and 14 (12 ± 1.5). They were sharply tuned to a single frequency. The BFs of these thalamic neurons ranged from 15 to 55 kHz ($m \pm SD$: 30 ± 3.9 kHz). The mean BF was not different between the 15 broadly tuned and 26 sharply tuned neurons. Four thalamic neurons had a Q-30 dB value between 6.0 and 9.0 and are classified as intermediately tuned. The intermediately tuned neurons could be classified as the sharply tuned ones. As described later, however, they showed large facilitation and no BF shifts for the MGB

electric stimulation, different from the sharply tuned neurons. When broadly tuned and sharply tuned neurons were simultaneously recorded with an electrode assembly, they were always at the electrodes located medially and laterally, respectively.

These three types of thalamic neurons were differently distributed in the coronal plane across the MGB (Fig. 5*B*). That is, the broadly tuned neurons were located 1.3–1.7 mm lateral from the midline (open circles), whereas the sharply tuned ones were located 1.7–2.3 mm lateral from it (filled circles). The intermediately tuned neurons (Fig. 5, x symbols) were located 1.7–1.9 mm lateral from it. All these neurons were located at depths between 2.7 and 3.3 mm from the surface of the posterior portion of AI. In terms of the properties of the frequency tuning and anatomical locations, the broadly tuned and sharply tuned neurons may hereafter be called MGBm and MGBv neurons, respectively. In the following, we focus on the effect of electric stimulation of MGBm or MGBv neurons on the frequency tuning of single cortical auditory neurons. As described above, there was no difference in BF between these two groups of thalamic neurons studied, so the difference between these groups in Q-30 dB was not due to any difference in BF.

The BFs of 66 cortical neurons studied ranged from 14 kHz to 45 kHz ($m \pm SD$: 31 ± 1.4 kHz), and their Q-30 dB values were unimodally distributed from 6.2 to 13 (11.5 ± 1.1). According to the above definition, 29 neurons out of the 66 were sharply tuned and the remaining 37 neurons were intermediately tuned (Fig. 5*C*). Electric stimulation of the thalamic neurons changed the distribution of the Q-30 dB values of the cortical neurons: 43 neurons were intermediately tuned, 17 neurons were sharply tuned, and the remaining six neurons were broadly tuned (Fig. 5*B*). The increase in the number of the intermediately tuned neurons was mostly due to the stimulation of the MGBm and intermediately tuned neurons. The

creation of six broadly tuned neurons was all due to the stimulation of the MGBm neurons.

Changes in the Q-30 dB values of the cortical neurons elicited by electric stimulation of the thalamic neurons are plotted in Figure 6A as a function of the Q-30 dB values of the thalamic neurons. The cortical neurons were first grouped into BF-matched (filled triangles) and -unmatched neurons. Then, the BF-unmatched neurons were further divided into two groups: BF-shifted (filled circles) and -unshifted (open circles). Electric stimulation of the MGBv neurons with a Q-30 dB larger than 9.0 evoked a BF shift in 18 cortical neurons (filled circles) and no BF shift in another 18 cortical neurons (open circles). The electric stimulation slightly broadened the cortical frequency-threshold curves, so that the decrease in a Q-30 dB was $3.3 \pm 4.5\%$ for the BF-shifted neurons and $2.8 \pm 3.9\%$ for the BF-unshifted ones. The difference between these two percentage changes was insignificant ($p < 0.05$). On the other hand, electric stimulation of the MGBm neurons with a Q-30 dB value < 6.0 and of the MGB neurons with a Q-30 dB between 6.0 and 9.0 broadened 17 cortical frequency-threshold curves without BF shifts (open circles). An average decrease in a Q-30 dB was $21 \pm 11.1\%$. Eight BF-matched cortical neurons showed neither BF shifts nor broadening of tuning curves, but two of them showed sharpening of their tuning curves (filled triangles).

BF shifts depend on the difference in BF between the recorded and stimulated neurons. In the big brown bat, they were not observed when the difference is larger than 10 kHz (Ma and Suga, 2001a). Therefore, all the data shown in Figure 6A were replotted in Figure 6B, where the ordinate represents BF differences instead of changes in Q-30 dB values. In Figure 6B, two horizontal dashed lines indicate the 10 kHz BF difference between the recorded cortical and stimulated thalamic neurons. For the BF differences < 10 kHz and for the stimulated MGBv neurons, 17 BF-unmatched cortical neurons showed a BF shift and 9 BF-unmatched cortical neurons showed no BF shift. Therefore, we may conclude that sharply tuned MGBv neurons evoked the BF shift in AI, whereas the broadly tuned MGBm neurons evoked nonspecific augmentation in AI.

Changes in response magnitude of the cortical neurons evoked by electric stimulation of the thalamic neurons were also examined at the BFs of the cortical neurons in the control condition as the function of Q-30 dB values of the thalamic neurons (Fig. 6C). Electric stimulation of the 17 MGBm and four intermediately tuned MGB neurons increased the responses of the 17 cortical neurons except for one (Fig. 6C, open circles). The amount of the augmentation at the BF and 30 dB above the minimum threshold ranged between 0.0% and 30% ($15.1 \pm 7.63\%$). On the other hand, electric stimulation of MGBv neurons reduced the responses of 15 out of the 18 BF-unmatched and -shifted cortical neurons by $10 \pm 22\%$ ($7.1 \pm 7.03\%$), increased the response of one out of the 18 by 10%, and did not change that of the remaining two (Fig. 6C, filled circles). Electric stimulation of the MGBv neurons increased or decreased the responses of the

Figure 5. Distributions of Q-30 dB values of MGB (A) and AI neurons (C,D) and recorded/stimulated sites of MGB neurons in the coronal plane across the MGB (B). A, C, Q-30 dB values of MGB neurons and AI neurons in the control condition, respectively. D, Q-30 dB values of AI neurons after electric stimulation of MGB neurons. In B, the different symbols indicate MGB neurons that were different in Q-30 dB values. Filled and open circles, Sharply tuned and broadly tuned MGB neurons, respectively. Crosses, Intermediately tuned MGB neurons. See the inset. N, The number of neurons studied. Q-30 dB is the quality factor indicating the sharpness of a tuning curve.

BF-unmatched and -unshifted cortical neurons (Fig. 6C, open circles). The mean change was $0.8 \pm 6.09\%$ (open circles). The BF-matched cortical neurons increased their responses by ~ 0 –19% ($7.0 \pm 5.8\%$) when the MGBv neurons (filled triangles) were electrically stimulated. The cortical changes evoked by electric stimulation of the intermediately tuned neurons were different from those evoked by the stimulation of the MGBv neurons: the change in Q-30 dB was $-13.0 \pm 0.01\%$ for the former, but $-4.0 \pm 0.08\%$ for the latter ($p = 0.02$) and the change in response magnitude was $18.0 \pm 5.70\%$ for the former, but $4.1 \pm 7.20\%$ for the latter ($p = 0.001$).

Discussion

Our current data and the models proposed for the role of MGBv and MGBm in evoking cortical plasticity

It has been repeatedly reported that MGBv neurons are sharply tuned whereas MGBm neurons are broadly tuned and often multip peaked (Aitkin, 1973; Calford, 1983; Bordi and LeDoux, 1994a,b). However, some MGBm neurons are relatively narrowly tuned (Edeline and Weinberger, 1992). Focal electric stimulation of the MGBv evokes BF shifts in AI in the mouse (Jafari et al., 2007) and big brown bat (our current paper). Focal electric stimulation of the central nucleus of the inferior colliculus evokes collicular BF shifts through MGBv, AI, and the corticocollicular projection (Zhang and Suga, 2005). The MGBv shows BF shifts for auditory fear conditioning (Edeline and Weinberger, 1991) and electric stimulation of AI (Zhang et al., 1997; Zhang and Suga, 2000). Therefore, the MGBv undoubtedly is involved in evoking the cortical BF shift.

MGBm neurons of the guinea pig show a BF shift for conditioning (Edeline and Weinberger, 1992). Does this mean that they evoke the cortical BF shift? It had not been examined whether electric stimulation of the MGBm of the guinea pig evoked the cortical BF shift. In our current experiments, we demonstrate that electric stimulation of MGBm neurons

Figure 6. Changes in the sharpness (Q-30 dB) of the frequency-threshold curves of AI neurons as a function of the sharpness of stimulated MGB neurons (**A**), the distribution of BF-shifted and BF-unshifted AI neurons in the coordinates of the BF differences between the recorded AI and stimulated MGB neurons and the sharpness of the stimulated MGB neurons (**B**), and changes in the response magnitude of AI neurons (**C**) at their BF and 30 dB above their minimum thresholds in the control condition as a function of the sharpness of the stimulated MGB neurons. Filled triangles, BF-matched AI neurons. Filled circles, BF-unmatched and -shifted AI neurons. Open circles, BF-unmatched and -unshifted AI neurons.

evokes the nonspecific augmentation, not the BF shift, of AI neurons.

Our current data are directly related to the circuit models proposed for the explanation of cortical tone-specific plasticity, i.e., BF shifts. Weinberger (1998, 2004) hypothesized that MGBm/PIN evokes the cortical BF shifts only after CS–US association occurs in the MGBm/PIN. In contrast, Gao and Suga (1998) hypothesized that the MGBm/PIN is not involved in evoking the cortical BF shift. Then Suga (2008) further hypothesized that the MGBv and MGBm/PIN are respectively involved in evoking the cortical BF shift (Fig. 7) and nonspecific augmentation (sensitization). The Gao-Suga and Suga models are thus fundamentally different from the Weinberger model. It is clear that our current data support the Gao-Suga and Suga models. In addition, there have been many neurophysiological findings indicating that the large long-term cortical BF shift can be evoked without the activation of the MGBm/PIN by both CS and US (Gao and Suga, 1998; Kilgard and Merzenich, 1998; Weinberger and Bakin, 1998; Yan and Suga, 1998; Ma and Suga, 2001, 2003; Yan and Zhang, 2005; Zhang and Suga, 2005; Jafari et al., 2007; Puckett et al., 2007; Wu and Yan, 2007).

All these three models recognize that ACh released into AI

Figure 7. Two models explaining the BF shifts evoked by auditory fear conditioning. **A**, Gao-Suga model: the MGBv is involved in evoking the cortical tone-specific plasticity, i.e., BF shifts. **B**, Weinberger model: the MGBm/PIN is involved in evoking the cortical BF shift only after CS–US association occurs in the MGBm/PIN. In both models, ACh augments the BF shift. ACh, Acetylcholine; AI, primary auditory cortex; CS, conditioning stimulus; IC, inferior colliculus; MGBm and MGBv, the medial and ventral divisions of the medial geniculate body; PIN, posterior intralaminar nucleus; SI, primary somatosensory cortex; TRN, thalamic reticular nucleus; US, unconditioned stimulus.

from the nucleus basalis (NB) augments the small cortical BF shift and changes it into the large long-term BF shift. However, how the NB is activated is different between the Weinberger and Gao-Suga models. In the Weinberger model, the MGBm/PIN sends the CS–US “associated” signal to not only AI but also to the amygdala, which in turn activates the NB. On the other hand the Gao-Suga model states that AC and the somatosensory cortices respectively send CS and US signals to the amygdala, which in turn sends the CS–US associated signal to the NB.

Whether the neural mechanisms found in the big brown bat are shared with nonbat species

In general, the auditory system of animals is specialized for detecting, processing, and localizing species-specific sounds and sounds produced by prey and predators. Therefore, the auditory system of bats must be specialized for processing biosonar information. This is a common understanding even though one may not know the data indicating it. The auditory system of the mustached bat, *Pteronotus parnellii*, is one of the best examples of such specialization. Its central auditory system contains two highly specialized subsystems for processing echo delays or Doppler shifts (for review, see Suga, 1990). In the auditory system of the big brown bat, however, it is not clear whether subsystems exist that are specialized for echolocation. There must be differences in the neurophysiological properties of the auditory system between the big brown bat and nonbat species. The differences may be quantitative rather than qualitative.

Compared with nonbat auditory neurons, bat auditory neurons generally respond to higher frequency sounds, respond best to shorter acoustic signals, and respond well to sounds delivered at high repetition rates. However, it is not clear whether the bat data are fundamentally different from the nonbat data because there is no sufficient data for such a comparison. On the other hand, it is easy to enumerate identical or similar data obtained from bat and nonbat species. Therefore, in relation to our current

research, we enumerate the following facts indicating that the auditory system of the big brown bat shares the identical or similar neurophysiological and morphological properties with that of nonbat species.

(1) As in cats (Imig and Morel, 1883) and rats (Clerici and Coleman, 1990; Clerici et al., 1990), the auditory thalamus consists of multiple nuclei (for review, see Wenstrup and Grose, 1995; our current observation).

(2) As in cats (Aitkin, 1973; Calford, 1983), MGBv and MGBm neurons show sharp and broad frequency-tuning curves, respectively (our current findings).

(3) As in cats (Katsuki et al., 1959; Calford et al., 1983), frequency-tuning curves tend to be broader in AI than in the MGBv (our current findings).

(4) As in the house mouse (Jafari et al., 2007), electric stimulation of MGBv neurons evokes cortical “centripetal” BF shifts, i.e., shifts toward the BF of the stimulated neurons (our current findings).

(5) As in cats and rodents, its AI has a high-to-low frequency axis along the anteroposterior axis of AI (Jen et al., 1989; Dear et al., 1993).

(6) As in the Mongolian gerbil (Sakai and Suga, 2002), focal electric stimulation of AI evokes the center-surround reorganization of the tonotopic-map of AI (Ma and Suga, 2004).

(7) As in the guinea pig (for review, see Weinberger, 1998), auditory fear conditioning elicits cortical and subcortical centripetal BF shifts, i.e., shifts toward the frequency of a conditioned tonal stimulus (Gao and Suga, 2000; Ji et al., 2001).

(8) As in the guinea pig (for review, see Weinberger, 1998) and house mouse (Yan and Ehret, 2002; Yan and Zhang, 2005; Jafari et al., 2007), the cortical and subcortical BF shifts are evoked by focal electric stimulation of the ICc (Zhang and Suga, 2005) or AI (Ma and Suga, 2001a, 2003) or conditioning (Gao and Suga, 2000; Ji et al., 2001) and are augmented by electric stimulation of the nucleus basalis (Ma and Suga, 2003) or by ACh applied to AI (Ji et al., 2001, 2005; Ma and Suga, 2005).

(9) As in the guinea pig (for review, see Weinberger, 1998), the cortical BF shift evoked by the conditioning slowly develops after the conditioning and is long-lasting (Gao and Suga, 2000), and this long-lasting BF shift is due to ACh released into the cortex by the NB (Ji et al., 2001, 2005; Ma and Suga, 2005).

(10) As in the guinea pig (Bakin et al., 1992), pseudoconditioning (unpaired CS and US) elicits nonspecific augmentation (sensitization) in the central auditory system (Ji and Suga, 2008).

(11) The plastic changes in the highly specialized auditory subsystems of the mustached bat are based on the basically identical neural mechanism shared with the auditory systems of many species of mammals including the big brown bat [for review, see Suga and Ma (2003) and Suga (2008)], and with the visual (Tsumoto et al., 1978; Murphy et al., 1999) and somatosensory (Malmierca and Nuñez, 1998; Canedo and Aguilar, 2000) systems.

(12) Duration-tuned neurons are found not only in several species of bats (Pinheiro et al., 1991; Casseday et al., 1994; Galazyuk and Feng, 1997; Ma and Suga, 2001b), but also in cats (He et al., 1997), chinchillas (Chen, 1998), mice (Brand et al., 2000), and frogs (Potter, 1965; Feng et al., 1990; Gooler and Feng, 1992).

(13) FM-sensitive neurons are found not only in several species of bats (Suga, 1965; Fuzessery, 1994), but also in the gerbil (Wetzel et al., 1998), rat (Poon et al., 1991), cat (Glaser, 1971), and monkey (Allon et al., 1981).

(14) Since bats are unique in echolocation, one may be unaware that they use many different types of communication calls, at least 33 types in the mustached bat (Kanwal et al., 1994). In contrast, there is usually only one type of species-specific echolocation call/species. The bats must process these complex calls, as primates do. In the mustached bat, it has been demonstrated that the neurons in the subsystems highly specialized for processing biosonar information respond to its communication calls (Ohlemiller et al., 1996; Kanwal et al., 1999). The bat’s auditory system must have the “common” auditory mechanism for processing communication calls. In addition it has the specialized mechanism for processing biosonar signals derived from this common auditory mechanism. The data presented in our current paper are not particularly related to echolocation and indicate a general principle for modulation of the sensory cortex by thalamic sensory neurons.

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