Corticothalamic Feedback for Sound-Specific Plasticity of Auditory Thalamic Neurons Elicited by Tones Paired with Basal Forebrain Stimulation

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Recent studies have revealed that the auditory cortex (AC) plays a crucial role in the plastic changes in the physiological properties of subcortical auditory neurons through corticofugal projections. In this study with the C57 mouse, we investigated the receptive field plasticity of the ventral division of the medial geniculate body (MGBv) of the thalamus and the impact of the primary AC using the electrical stimulation of the cholinergic basal forebrain, the nucleus basalis, paired with a tone (tone-ESNB). We found that tone-ESNB evoked significant changes in MGBv receptive fields; the best frequencies (BFs) of MGBv neurons shifted toward the frequency of the paired tone. The BF shifts of MGBv neurons were maximal when the difference between the BFs of MGBv neurons and the frequency of the paired tone was 7 kHz. In addition to the BF shifts, the minimum threshold was decreased and the spike number was increased in response to the paired tone. Importantly, these plastic changes of MGBv neurons were completely abolished when the AC was inactivated with a cortical application of muscimol, a γ-aminobutyric acid receptor subtype A receptor agonist. Our data indicate that the corticofugal system is an essential neural substrate for the sound-specific plasticity in the auditory thalamus.

Keywords: auditory cortex, basal forebrain, corticofugal, medial geniculate body, plasticity

Introduction

Visual, auditory, and somatosensory information acquired by the sensory cortices are exclusively relayed through the thalamus. The massive reciprocal feedback from the cortex to the thalamus (Deschenes et al. 1998; Winer et al. 2001; Rouiller and Durif 2004) suggests that central processing of sensory information is far more intricate than the traditional notion of hierarchical feed-forward processing. Our relatively poor understanding of the cortical impact on thalamic function may have limited our view of sensory information processing and cognition.

Behavioral studies of sound discrimination have found that there is an interesting relationship between the auditory cortex (AC) and the medial geniculate body (MGB) of the thalamus. Animals typically experience immediate and complete disruption in sound frequency discrimination after transient and reversible inactivation of the AC (Riquimaroux et al. 1991; Talwar et al. 2001). The ability of frequency discrimination can completely resume when cortical inactivation is restored (Talwar et al. 2001). In contrast, animals show little deficit in sound frequency discrimination after a few days or weeks recovery from lesion of the AC (Pickles 1998; Ohl et al. 1999; Ono et al. 2006). These behavioral findings are in concert with electrophysiological reports that the focal activation of the AC modulates subcortical activities in a highly specific manner (Yan and Suga 1996; Zhang and Suga 1997; Zhou and Jen 2000; Yan and Ehret 2002; Jen and Zhou 2003), whereas global inactivation of the AC reduces the auditory response and frequency selectivity of MGB neurons (Villa et al. 1991; Zhang and Suga 1997; Zhang, Dyck, et al. 2005). These data strongly suggest that the MGB potentially processes auditory information independently of the AC. In nature, however, auditory information processing in the MGB must be under the control or regulation of the AC.

The continuous interest in the neural basis of auditory learning and experience has encouraged further investigations in sound-specific auditory plasticity in the brain. Physiological studies are concluding that auditory learning or experience causes sound-specific retuning of neuronal receptive fields not only in the AC but also in subcortical nuclei (Bakin and Weinberger 1990; Edeline and Weinberger 1991; Lennartz and Weinberger 1992; Gao and Suga 2000). The existence of topographically organized corticothalamic fibers (Winer et al. 2001) and frequency-specific corticothalamic modulation (Zhang and Suga 2000) suggests a potential involvement of the corticothalamic feedback in sound-specific plasticity of the thalamic neurons evoked by auditory learning and/or experience.

The purpose of our present study is to clarify the importance of the AC in thalamic plasticity evoked by the electrical stimulation of the nucleus basalis (NB) of the basal forebrain paired with tone (tone-ESNB). It has been established that the NB is the major cholinergic source of the cerebral cortex and is extensively involved in the learning-induced or experience-dependent auditory plasticity. Tone-ESNB induces tone-specific shifts of the receptive fields of cortical and collicular neurons (Bakin and Weinberger 1996; Kilgard and Merzenich 1998; Ma and Suga 2003; Yan and Zhang 2005; Zhang, Dyck, et al. 2005). Our current data show that tone-ESNB induces highly specific changes in the receptive fields of thalamic neurons and that these changes can be eliminated by cortical inactivation with muscimol, an agonist of γ-aminobutyric acid receptor subtype A.

Materials and Methods

Procedures for acoustic stimulation, recording of neuronal activities, NB stimulation, data acquisition, and data analysis are described elsewhere (Yan and Zhang 2005; Zhang et al. 2006; Jafari et al. 2007). The essential portions of our methods are summarized below. Experimental procedures were in accordance with the Canadian Council on Animal Care and approved by the Animal Care Committee of the University of Calgary (Protocol Number M02014).

General

In this study, we used 49 C57 female mice (Charles River Laboratories, Senneville, Canada) that were 5–6 weeks old and weighed 15.4–21.7 g.
All surgeries and physiological experiments were performed under anesthesia by intraperitoneal injection of the mixture of ketamine (100 mg/kg) and xylazine (20 mg/kg). Additional doses of the ketamine (20 mg/kg) and xylazine (3.5 mg/kg) mixture were administered when the animal showed any response to pinching of its paw or tail. Under anesthesia, the head was immobilized with a custom-made head holder and the skull was surgically exposed. A hole of 1.0 mm in diameter and 1.2 mm posterior to the bregma and 1.8 mm left to the midline was made in the skull for the placement of a stimulating electrode to the NB (Franklin and Paxinos 1996). The skull and dura covering the left primary AC to allow the application of either saline or muscimol. Vaseline was applied to the bottom rim of the tubing to prevent the spread of drugs over the brain surface (Yan and Suga 1999; Zhang, Hakes, et al. 2005). Two additional holes measuring 1 mm in diameter were made on the right side of the midline, 1 posterior to the bregma and the other anterior to the lambda for electroencephalogram (EEG) recordings. The body temperature of the animal was maintained at 37°C with a feedback-controlled heating pad. All electrophysiological experiments were performed in a soundproof and echo-attenuated room.

**Acoustic Stimulation**

Tone bursts of 60 ms in duration and 5 ms in rise/fall time were digitally synthesized and converted to analog sinusoid waveforms using RPvdsEx software and a RP2 real-time processor (Tucker-Davis Tech., IL). The output amplitude of the RP2 real-time processor was 20 volts peak-to-peak. The signals were then fed to a PAS digital attenuator. Through a power amplifier, the tone bursts were delivered from a leaf tweeter (EAS-10TH800, Matsushita Electric Co. Ltd., Japan) that was placed 45 cm away from the subject. A tungsten electrode of the threshold current for EEG desynchronization (Yan and Zhang 2005) was surgically exposed. A hole of 1.0 mm in diameter and 1 mm in height was placed on the surface of the brain that covered the primary AC to allow the application of either saline or muscimol. The skull and dura covering the left primary AC as well as the ventral division of the left MGB (MGBv) was removed to permit the cortical application of drugs and the placement of a recording electrode. The coordinates for the MGBv were 5.1 mm posterior to the bregma, 1.8 mm left to the midline, and ~3.0 mm below the brain surface (Franklin and Paxinos 1996). Polyethylene tubing (1.5 mm in diameter and 1 mm in mm in height) was placed on the surface of the brain that covered the primary AC to allow the application of either saline or muscimol. Vaseline was applied to the bottom rim of the tubing to prevent the spread of drugs over the brain surface (Yan and Suga 1999; Zhang, Hakes, et al. 2005). Two additional holes measuring 1 mm in diameter were made on the right side of the midline, 1 posterior to the bregma and the other anterior to the lambda for electroencephalogram (EEG) recordings. The body temperature of the animal was maintained at 37°C with a feedback-controlled heating pad. All electrophysiological experiments were performed in a soundproof and echo-attenuated room.

**Electrical Stimulation of the Nucleus Basalis**

EEG recording was required for examining the efficiency of the NB activation. The EEG was recorded with 2 silver electrodes placed on the dura close to the bregma and lambda, filtered with a bandpass of 3–100 Hz and amplified 10 000 times. The signals were then sent to an oscilloscope for observation and to a computer equipped with SciWork software (DataWave Techs, Berthoud, Colorado, USA). A concentric bipolar electrode was advanced about 4.5 mm to the NB through a hole made in the skull. The NB was stimulated by a train of electrical pulses (0.2 ms long, monophasic square wave, 120 Hz, 200 ms train duration) generated by a stimulator (Grass S88, Astro-Medical, Inc., West Warwick, Rhode Island, USA) and a constant current unit (Grass CUC1, Astro-Med, Inc.). The current pulses were delivered through the central pole of the concentric electrode. To determine the position of the electrode tip for optimal stimulation, 5 trains of electrical pulses were used as testing stimuli. The position of the electrode tip was adjusted until the maximal desynchronization of the EEG was achieved. Then the stimulus current for the ESNb was set at 10 μA above the threshold current for EEG desynchronization (Yan and Zhang 2005).

**Recording of Tone-Evoked Neuronal Activities in the MGBv**

A tungsten electrode of -2 MΩ impedance was dorsoventrally inserted into the MGBv according to the stereotaxic coordinates of the MGBv. Action potentials picked up by the recording electrode were filtered with a 0.3–10 kHz bandpass and amplified 10 000 times by the RA16 Medusa Base Station (Tucker-Davis Tech.). These signals were stored using BrainWare data acquisition software (Tucker-Davis Tech.) and simultaneously sent to an oscilloscope for observation.

Once the recording electrode was positioned approximately 2 mm below the brain surface, a tone burst with manual alteration of frequency and amplitude was delivered to the animal at a rate of 1 per second. Once neuronal responses to a tone stimulus were observed, the electrode was further advanced until no auditory response was recorded. This point represented the ventral border of the MGBv. Then the electrode was slowly withdrawn by 50-100 μm and the responses of thalamic neurons to the FA-scan were recorded. If the recorded neurons were not sharply tuned to a particular frequency, the electrode was withdrawn and another penetration was made until sharply tuned neurons were recorded. Sharply tuned neurons were frequently located at about 3 mm below the brain surface. This method ensured that our electrode tip was within the MGBv, a decision well-justified by the histological examination of the lesion mark of brain sections (Jafari et al. 2007). The neuronal response to the FA-scan was then recorded.

**Application of Muscimol to the AC**

Our study and others demonstrate that cortical application of muscimol eliminates corticofugal activities (Zhang and Suga 1997; Yan and Suga 1999; Ma and Suga 2003; Zhang, Dyck, et al. 2005). In this study, muscimol (1 mg/mL) was dropped onto the polyethylene well that was placed on the AC with a 1–2 mm drop below the primary AC and was washed out with 0.9% saline just after the cessation of the tone-ESNb. In the control group, 0.9% saline was applied to the cortical surface in the same manner as the muscimol application.

**Experimental Protocols and Data Acquisition**

Once the concentric electrode was optimally placed for electrical stimulation of the NB and the recording electrode sampled the auditory responses of a few units (multunit recording), the responses of MGBv neurons to the FA-scans were recorded before and after cortical application of saline or muscimol. The animal then received tone-ESNb. The ESNb was synchronized at the onset of tone burst and delivered to the animal at a rate of 1 per second for 6 min. The frequency of the tone paired with ESNb (hereafter, paired tone) was set in a range between 10 kHz higher and lower than the best frequency (BF) and the amplitude was set at 20 dB above the minimum threshold (MT) of a given MGBv neuron. The responses of the MGBv neuron to the FA-scans were recorded immediately after and every 30 min after delivery of the tone-ESNb.

Once the physiological experiments were completed, a 1 mA, 30-s-long electrical current was applied to the stimulating site in the NB and the recording site in the MGBv in order to make a small lesion at each of these sites. Under deep anesthesia, the animal was given a cardiac perfusion of 10% formalin. The brain was then embedded by paraffin. Coronal sections of the brain were made at 10-μm thickness and stained with hematoxylin-eosin. The electrolytic lesions were examined under a light microscope.

**Data Processing**

Multunit recording data were analyzed with custom-made software. Single units were isolated according to the waveform of action potentials, which measured 8 parameters of the action potential waveform, that is, peak, valley, spike height, spike width, peak time, valley time, and 2 user-defined voltage values. Separated clusters of action potentials were commonly displayed when scatter plotting was made by using any 2 of these parameters as coordinates. Separated clusters were then grouped. Each of cluster represented action potentials that had similar waveform and considered to be from a single unit. Subsequent data processing was based on isolated single units. The responses of single MGBv neurons to the FA-scans were displayed by dot-rasters, poststimulus-time histograms or cumulative peristimulus time histograms, all with a bin width of 1.0 ms. The BF, MT, and receptive field (the area inside of a frequency tuning curve) of the
MGBv neuron were determined based on the neuronal responses to EA-scan. The MT was the lowest response threshold across all frequencies. The BF was the frequency at the MT. The receptive field was derived from the response threshold to each frequency (Yan and Ehret 2002; Yan and Zhang 2005). The MGBv plasticity was determined by comparing the receptive fields of the MGBv neuron obtained before and after tone-ESNB. For contour plotting, the dB SPL measured at different frequencies was rounded up or down to the nearest 5.

For statistical analysis, data were expressed as mean ± standard deviation. A student’s t-test was used to examine the significance of the differences between 2 sets of data. A P value of less than 0.05 was considered to be statistically significant.

Results
As previously reported (Yan and Zhang 2005; Zhang, Hakes, et al. 2005; Zhang et al. 2006), the global EEG showing large/slow waves under anesthesia changed to small/fast waves when the NB was electrically stimulated. This EEG desynchronization suggested that the NB was activated by electrical stimulation.

In total, 86 thalamic neurons were studied; 53 neurons were recorded from 30 mice administered a cortical application of saline and 33 neurons were recorded from 19 mice administered a cortical application of muscimol. All the recorded neurons were sharply tuned to specific frequencies. Their BFs ranged from 9 to 35 (17.93 ± 5.41) kHz and their MTs ranged from 3.2 to 35.9 (19.59 ± 7.88) dB SPL. They were tuned to the frequencies within the central hearing range of C57 mice (Zhang, Dyck, et al. 2005).

Effects of Tone-ESNB on the Thalamic Receptive Fields
Tone-ESNB induces robust changes in the cortical receptive field. Cortical BFs shift toward the frequency of the paired tone; the tone-specific BF shift is largely attributed to the frequency-specific threshold decrease (Yan and Zhang 2005). Therefore, we first examined the changes in thalamic receptive fields elicited by the tone-ESNB. The neuron in Figure 1 illustrates the changes in auditory response and receptive field of a MGBv neuron. This neuron was tuned to 20 kHz with an MT of 16 dB SPL (Fig. 1A). Electrical stimulation of the NB paired with a 26-kHz tone induced changes in its receptive field. The threshold to a 20-kHz tone increased from 16 to 31 dB SPL, whereas the threshold to a 25-kHz tone decreased from 30 to 15 dB SPL. Due to these changes, the BF of the neuron shifted from 20 to 25 kHz, that is, toward the frequency of the paired tone (Fig. 1B). We observed the receptive field change over 5 h after the tone-ESNB. The BF of the neuron shifted back to 20 kHz 300 min after the tone-ESNB (Fig. 1C).

To evaluate the BF changes of all sampled neurons, we plotted the BF shifts as a function of the difference between the control BFs of thalamic neurons and the frequencies of the paired tones. As shown in Figure 2, the thalamic BFs showed an orderly change after tone-ESNB. The tone-ESNB shifted thalamic BFs higher when the frequencies of the paired tones were higher than thalamic BFs. On the other hand, the tone-ESNB shifted thalamic BFs lower when the frequencies of the paired tones were lower than thalamic BFs. The thalamic BFs were not altered when they were less than 1 kHz different from the frequencies of the paired tones. The BF shifts evoked by tone-ESNB were significantly correlated to the differences between the frequencies of the paired tones and the control BFs of thalamic neurons (n = 53, y = -0.41x + 0.06, r = 0.74, P < 0.001). These data indicate that tone-ESNB evoked centripetal BF shifts for an expanded representation of the frequency of the paired tone in the MGBv. Figure 2 also shows that there was a linear relationship of the centripetal BF shift and the difference between tone frequency and thalamic BF when the difference was equal to or less than 7 kHz (slope = 0.41). The thalamic BF shifts beyond the 7.0 kHz difference were small and the slope of the regression line was 0.29.

We also measured the changes in response thresholds at the control BFs and shifted BFs (Fig. 3). In general, tone-ESNB decreased thalamic MT by 3.0 ± 5.1, from 18.5 ± 8.4 dB SPL (threshold at control BF before tone-ESNB) to 15.6 ± 8.7 dB SPL (threshold at shifted BF after tone-ESNB). The change was statistically significant (P < 0.001). Tone-ESNB increased the response threshold at the control BF by 3.4 ± 4.1 dB (P < 0.001).
Effects of Cortical Inactivation on Thalamic Auditory Responses

A muscimol application to the AC inactivates cortical neurons and functionally eliminates corticofugal feedback (Zhang and Suga 1997; Yan and Suga 1999; Talwar et al. 2001; Zhang, Hakes, et al. 2005). Figure 4 shows that cortical inactivation with muscimol did not evoke a BF shift but reduced the auditory responses of a MGBv neuron at its BF (Fig. 4Aa–d and Ba–b). On average, the BFs of 33 recorded MGBv neurons were 18.22 ± 4.65 kHz before and 18.25 ± 4.63 kHz after a muscimol application. Although cortical inactivation slightly increased thalamic MTs from 20.14 ± 9.25 to 22.19 ± 9.62 dB SPL, this increase was statistically insignificant (P > 0.05, Fig. 5Aa). In the 33 MGBv neurons, the spike number per 5 tonal stimuli measured at the BF and 10 dB above the MT was reduced from 10.22 ± 6.17 to 7.16 ± 4.56 by muscimol application to the AC (P < 0.05, Fig. 5Ac).

Time Course of BF Shift Evoked by Tone-ESNB

Tone-ESNB accompanied with a saline application quickly induced the changes in thalamic BFs. Out of 48 neurons that showed a BF change after tone-ESNB, the BFs of 11 (20.3%) neurons shifted back to their original BFs 150 min after the tone-ESNB, and those of 36 (75.0%) neurons shifted back to their original BFs 300 min after the tone-ESNB. On the average, the BF shift achieved its maximum level in 30 min and then gradually shifted back to the control BF. A 50% recovery occurred at 120–150 min and a 90% recovery occurred at 270 min after tone-ESNB (Fig. 6, solid circles). This time course was similar to those of the cortical and collicular BF shifts evoked by tone-ESNB.

Discussion

The functional organization of the central auditory system can be altered by acoustic signals if these signals are repeatedly presented or behaviorally relevant. Increasing evidence shows that auditory learning improves the neural processing of learned sensory information; that is, the central representation of learned sensory information is enhanced. Studies with animal models demonstrate that auditory learning or experience shifts the receptive fields of auditory neurons toward the frequency of the learned sound in the AC, MGB, and inferior colliculus (IC) of the midbrain (Bakin and Weinberger 1990; Gao and Suga 2000; Ji et al. 2001). Such highly tone-specific plastic changes can also be induced by focal electrical stimulation of the AC (Gao and Suga 1998; Yan and Suga 1998; Yan and Ehret 2002; Yan et al. 2005). Suga and his colleagues reveal that the IC plasticity induced by the cortical electrical stimulation can be augmented by fear conditioning, basal forebrain stimulation or a cortical application of acetylcholine (Gao and Suga 2000; Ma and Suga 2003, 2005). These findings suggest that corticofugal modulation is an important mechanism for learning-induced or experience-dependent auditory plasticity (Suga et al. 2002).
With the tone-ESNB, we previously demonstrated in mice that the plasticity of the AC and midbrain is highly specific to the frequency of the paired tone, because the cortical and collicular BFs shift toward the frequency of the paired tone (Yan and Zhang 2005; Zhang, Hakes, et al. 2005; Chen and Yan 2007). In this study, we found that the tone-ESNB evoked the tone-specific BF shifts of thalamic neurons (Figs 1–3 and 6). However, the amount of the thalamic BF shift (slope = 0.41) was smaller than that of the cortical BF shift (slope = 0.53, Yan and Zhang 2005) but larger than that of collicular BF shift (slope = 0.36, Zhang, Hakes, et al. 2005). Therefore, the frequency-specific BF shifts evoked by tone-ESNB are progressively increased from the midbrain to thalamus to cortex.

The receptive fields of cortical neurons are primarily determined by thalamocortical inputs (Miller et al. 2001; Metherate et al. 2005). Our recent study has shown that focal

**Figure 4.** Effects of cortical inhibition (A) and cortical inhibition plus tone-ESNB (B) on the thalamic receptive fields. The cortical application of muscimol decreased the response magnitude but did not change the BFs of these 2 neurons (Aa–d and Ba–b). When the AC was inhibited by muscimol (B), tone-ESNB did not alter the BF of this thalamic neuron (Bb and Bc). The arrowhead indicates the frequency of the paired tone. The thalamic receptive fields recovered to those of the controls 360 min after cortical application of muscimol (Aa and Ad) and 300 min after tone-ESNB (Ba and Bd).
number were significantly larger for tone-ESNB with saline (i.e., without muscimol) than for tone-ESNB with muscimol (B). The equation of the % of BF shift (Ba) was absolute change. *P < 0.05, compared with data before cortical application of muscimol; ***P < 0.001, comparing between saline and muscimol groups.

Figure 5. Changes in the BFs, MTs, and spike numbers of thalamic neurons after a cortical application of muscimol (A) or after tone-ESNB with cortical application of either saline or muscimol (B). The cortical application of muscimol significantly decreased the response magnitude (Ac). The changes in thalamic BF, MT, and spike number were significantly larger for tone-ESNB with saline (i.e., without muscimol) than for tone-ESNB with muscimol (B). The equation of the % of BF shift (Ba) was 100 × (BF shift/difference between tone frequency and thalamic BF). The MT change (Bb) was absolute change. *P < 0.05, compared with data before cortical application of muscimol; ***P < 0.001, comparing between saline and muscimol groups.

Figure 6. Time course of the percentage change in thalamic BF following tone-ESNB (black line with closed circles). The maximum thalamic BF changes occurred at 30 min after tone-ESNB. The thalamic BFs shifted back to the control BFs by 50% at 120–150 min and had almost recovered at 270–300 min after tone-ESNB. The dashed gray and solid gray lines represent the time courses of tone-ESNB-evoked BF changes of cortical neurons (Yan and Zhang 2005) and midbrain neurons (Zhang, Hakes, et al. 2005), respectively. P: prior to tone-ESNB, that is, control.

electrical stimulation of the MGBv changes the BF, MT, bandwidth, receptive field area, and averaged response magnitude of cortical neurons toward the values of the stimulated thalamic neuron (Jafari et al. 2007). This suggests that thalamocortical circuitry possesses an intrinsic mechanism for input-specific cortical plasticity induced by auditory learning or experience. Studies of the role of the NB in cortical plasticity also support this conclusion. NB activation facilitates thalamocortical synaptic transmission (Metherate and Ashe 1993). Cortical application of atropine, a muscarinic acetylcholine receptor antagonist, completely eliminates the cortical plasticity induced by tone-ESNB (Bakin and Weinberger 1996; Ma and Suga 2003; Yan and Zhang 2005). The cortical plasticity induced by tone-ESNB apparently results from the interaction of cholinergic and thalamocortical inputs within the AC; cortical plasticity does not result from subcortical plasticity (Chen and Yan 2007). Similar to previous findings (Zhang and Suga 1997; Yan and Suga 1999; Zhang, Hakes, et al. 2005), this study showed a decline of auditory response of thalamic neurons by cortical inactivation, suggesting a positive feedback from the AC to the MGBv through corticothalamic projections. Inactivation of the AC abolished the plastic changes in the thalamus (Figs 4 and 5). These findings allow us to conclude that auditory plasticity induced by the tone-ESNB mainly occurs at the AC through thalamocortical projections and that the thalamic plasticity inherits cortical plasticity through corticofugal projections.

In addition to corticothalamic projections, AC also sends large amount descending projections to subthalamic auditory nuclei, that is, the IC, lateral lemniscus, superior olivary complex, and cochlear nucleus (Saldana et al. 1996; Weedman and Ryugo 1996; Winer et al. 1998; Doucet et al. 2002; Coomes and Schofield 2004; Schofield and Coomes 2005). Highly frequency-specific corticofugal modulation of the thalamus and midbrain has been extensively studied in bats and mice (Yan and Suga 1998; Zhou and Jen 2000; Zhang and Suga 2000; Yan and Ehret 2002; Yan et al. 2005). Acoustic stimulation alone can evoke cortical and collicular plastic changes and the collicular plasticity is dependent on corticocollicular feedback (Gao and Suga 1998; Yan and Suga 1998; Chowdhury and Suga 2000; Suga and Ma 2003). Auditory learning and tone-ESNB have been shown to induce centripetal plasticity in the collicular neurons, which can be eliminated by the inactivation of the AC with muscimol (Gao and Suga 1998; Zhang, Hakes, et al. 2005). It is thus inferable that corticofugal projections also transfer cortical plasticity to subthalamic nuclei and the plasticity of the subthalamic nuclei, in turn, is forwarded up to the auditory thalamus and cortex through ascending projections. Therefore, the thalamic plasticity observed in the present study should be an integrative result of corticothalamic modulation, corticocollicular modulation, and cortico-subcollicular modulation.

Plasticity evoked by auditory learning or experience must be more complex than that evoked by tone-ESNB, because an arousing stimulus activates not only the NB but also other limbic structures. With regard to cholinergic influences on auditory plasticity, the cortex receives cholinergic inputs from the NB whereas the thalamus and midbrain receive cholinergic inputs from the brainstem, that is, the cholinergic thalgmental nuclei, pedunculopontine tegmental nucleus, and laterodorsal tegmental nucleus (Mesulam et al. 1983). These cholinergic nuclei, active during wakefulness, are also involved in learning process (Koyama et al. 1994; Inglis et al. 2000; Ivlieva and Timofeeva 2003). In bats, fear conditioning causes BF shifts of
cortical and collicular neurons toward the frequency of the conditioned tone. Cortical application of atropine abolishes cortical plasticity but only reduces collicular plasticity (Ji et al. 2001). This suggests that, different from the tone-E3SN, auditory fear conditioning induces auditory plasticity through not only the AC but also subcortical nuclei.

In conclusion, although sound-specific plasticity occurs in the AC and subcortical nuclei during learning, the AC is the major source of plastic changes; it has a profound influence on subcortical plasticity through reciprocal feedback. However, the development of learning-induced or experience-dependent plasticity in the AC and subcortical auditory nuclei must be coordinated through the incorporation of feed-forward ascending with feedback descending systems.

Funding
National Sciences and Engineering Research Council of Canada and the Campbell McLaurin Chair for Hearing Deficiencies of the University of Calgary.

Notes
The authors wish to thank Thayre C. Fellows for her help with the experiments described in this paper. Conflict of Interest: None declared.

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