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## An *in vivo* intracellular study of auditory thalamic neurons

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### Abstract

The intrinsic electrophysiological properties of medial geniculate body (MGB) neurons and their responses to noise bursts/pure tones were examined in the pentobarbital anesthetized guinea pig through intracellular recording. Discharge rate was calculated in the absence of acoustic stimuli over varied membrane potentials which were changed by intracellular injection of current or through automatic drifting. The non-acoustically-driven firing rate was  $45.8 \pm 23.3$  Hz (mean  $\pm$  S.D.,  $n = 8$ ) at membrane potentials of  $-45$  mV,  $30.6 \pm 19.4$  Hz ( $n = 14$ ) at  $-50$  mV,  $18.0 \pm 12.9$  Hz ( $n = 14$ ) at  $-55$  mV, and significantly decreased to  $5.7 \pm 7.4$  Hz at  $-60$  mV, and to  $0.7 \pm 1.5$  Hz ( $n = 10$ ) at  $-65$  mV (ANOVA,  $P < 0.001$ ). The maximum non-acoustically-driven rate observed in the present study was 160 Hz. The auditory responsiveness of the MGB neurons was examined at membrane potentials over a range of  $-45$  to  $-75$  mV: the higher the membrane potential, the greater the responsiveness and vice versa. A putative non-low-threshold calcium spike (non-LTS) burst was observed in the present study. It showed significantly longer inter-spike intervals ( $11.6 \pm 6.0$  ms,  $P < 0.001$ ,  $t$ -test) than those associated with the putative LTS bursts ( $6.7 \pm 2.4$  ms,  $P < 0.001$ ,  $t$ -test). The dependence of the temporal structure of the spikes/spike bursts on the stimulus may provide insight into the temporal coding of sound information in the auditory system.

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**Keywords:** Medial geniculate body; Action potential; Resting membrane potential; Current injection; Spontaneous firing; Tuning curve

### 1. Introduction

The auditory thalamus that relays information from the inferior colliculus to the cortex mainly includes the medial geniculate body (MGB) and the lateral part of the posterior nucleus group (Imig and Morel, 1983). The lemniscal core of MGB is the tonotopically organized ventral nucleus (MGv) (Aitkin and Webster, 1971; Clarey et al., 1992). The non-lemniscal MGB consists of the medial and the dorsal nuclei, where neurons show long latency, bursty firing, broad or no frequency tuning, non-tonotopic organization, and multi-modal responses (de Ribaupierre and Toros, 1976; Calford and Webster, 1981; Calford, 1983; Winer and Morest, 1983; Imig and Morel, 1988; Hu, 1995; He and Hashikawa, 1998; He and Hu, 2002).

As compared to the ascending thalamocortical projection, the MGB receives a much stronger reciprocal projection from the cortex (Andersen et al., 1980; Winer and Larue, 1987). This corticofugal projection has been suggested to provide a gating or gain-control mechanism in the transmission of information from the periphery to the cortex (Ryugo and Weinberger, 1976; Crick, 1984; Deschênes and Hu, 1990; Villa et al., 1991; Suga et al., 1997; Zhou and Jen, 2000). Different techniques have revealed that the stimulating auditory cortex exerts facilitatory and/or inhibitory modulation on the thalamic relay neuron, either directly via stimulated neurons or indirectly polysynaptically (Watanabe et al., 1966; Ryugo and Weinberger, 1976; Villa et al., 1991; He, 1997; Suga et al., 1997; Zhou and Jen, 2000; He et al., 2002).

Most of our understanding of the MGB has been obtained with extracellular electrophysiological recordings. Intracellular recordings on the thalamic slice have provided insights into the synaptic mechanisms of relay neurons in the MGB (Hu et al., 1994; Hu, 1995; Li et al., 1996; Tennigkeit et al., 1996, 1998; Bartlett and Smith, 2002). *In vivo* intracellular recording in the inferior colliculus has revealed a putative inhibitory mechanism for duration tuning in the bat, and complex interactions of excitatory and inhibitory input for binaural signal processing (Casseday

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et al., 1994; Kuwada et al., 1997). A recent *in vivo* intracellular study by Ojima and Murakami (2002) revealed that there are layer-specific differences in the auditory response characteristics of pyramidal neurons in the auditory cortex. However, little is known about the *in vivo* intracellular response characteristics to natural sound stimuli of MGB neurons.

The present study is aimed to record responses of relay neurons in the MGB in relation to alterations in their membrane potentials. We studied the non-acoustically-driven firing, the responses to auditory stimuli and to electrical current injection, and the changes in neuronal responses to auditory stimuli while the membrane potential was manipulated through current injection.

## 2. Methods

### 2.1. Animal preparation

Fifteen adult guinea pigs with clean external ears served as subjects. Sodium pentobarbital (40 mg/kg Nembutal initially, 5–10 mg/kg h, i.p.) was administered during surgical preparation and recording. An electrocorticogram from the left frontal cortex was used to monitor the anesthetic level of the animal. Atropine sulphate (0.05 mg/kg, s.c.) was given 15 minutes before anesthesia commenced and at regular intervals (0.01 mg/kg h, s.c.) during recording so as to minimize tracheal secretion. The preparation of the guinea pig has been described before (He, 2001). Briefly, the subject was mounted in a stereotaxic device following 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 the cortex, and to vertically access the MGB in the right hemisphere. The dura mater was removed above the auditory cortex and at a position vertically above the auditory thalamus. Before the left ear was freed from the ear bar, the head was fixed with two stainless steel bolts together with acrylic resin to an extended arm of the stereotaxic frame. These ensured that the subject's head remained fixed to the stereotaxic device without misalignment.

For effective intracellular recording, it is not difficult to penetrate the neuron with the recording electrode, but it is more challenging to maintain stable recording for a prolonged period. Since breathing causes alternate positive and negative thoracic pressure changes, which transfer to the brain and cause movement of the brain, artificial ventilation was used and the animal's muscles were relaxed with gallamine triethiodide (50 mg/kg, i.p.). To minimize the pressure in the chest, bilateral pneumothorax was done and the trunk of the animal was suspended on a spinal frame. Intra-cranial pressure was reduced by release of the cerebrospinal fluid through an opening of the dura mater at the foramen magnum. The procedures were approved by the Animal Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University.

### 2.2. Acoustic stimulus

Acoustic stimuli were generated digitally by a MALab system (Kaiser Instruments, Irvine, CA, USA), which was controlled by a Macintosh computer (Semple and Kitzes, 1993; He, 1997). 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 or longer and 5 ms rise/fall time were used to examine the neuronal responses.

### 2.3. Recording

We used a glass-pipette as the recording electrode which was filled with 1.0 M KCl. The resistance of the electrode was between 40 and 90 M $\Omega$ . The electrode was advanced vertically from the top of the brain by the stepping motor. After the electrode was lowered to 4–5 mm from the cortical surface, the cortical exposure was sealed by low-melting temperature paraffin. When the electrode was near or in the targeting area, it was then slowly advanced at 1 or 2 mm per step.

The MGB was stereotaxically accessed vertically from the top of the brain, according to a guinea pig brain atlas (Rapisarda and Bacchelli, 1977). The vertical coordinate of the electrode was determined with reference to the cortical surface at penetration. The electrode picked up the membrane potential showing negative value when it penetrated the membrane of a cell. After amplification, the membrane potential was recorded on a computer (AxoScope) which also simultaneously stored the auditory stimulus.

Membrane potentials were manipulated through the injection of either positive or negative current into the recording neuron. Positive current depolarized the neuron and negative current hyperpolarized it. The steady-state membrane potential stood for the baseline of the membrane potential when current was injected into the neuron. Pure tones and noise bursts were used as acoustic stimuli. Neuronal responses to the acoustic stimuli were recorded together with the responses to current injection. Low-threshold calcium spikes (LTS) were elicited when the membrane potential was hyperpolarized to below  $-75$  mV.

The time of spike occurrence relative to stimulus delivery was also stored in the Macintosh computer used as the stimulus controller by the MALab software. The computer automatically created raster displays of the responses, together with frequency response functions (responses to pure tones plotted as a function of frequency).

## 3. Results

Data presented here were obtained from 28 MGB neurons in 15 guinea pigs.

### 3.1. Spontaneous/non-acoustically-driven firing rate

The non-acoustically-driven firings increased when the membrane potential was depolarized and decreased when it was hyperpolarized. An example is showed in Fig. 1A. The neuron showed no spontaneous firings when its resting membrane potential was  $-63$  mV, and a very few non-acoustically-driven firings when the membrane potential was between  $-60$  and  $-56$  mV. The non-acoustically-driven firings dramatically increased when the resting membrane potential was depolarized to above  $-55$  mV as shown in the first row of Fig. 1A.

The highest non-acoustically-driven firing rate (spontaneous firing rate) observed in the present study was 160 Hz (data not shown in the Fig. 1) and the lowest was 0 Hz. The non-acoustically-driven firing rate depended on the membrane potential: the lower the membrane potential the lower the non-acoustically-driven firing rate and vice versa. This result was confirmed on all 23 neurons tested for this purpose in the present study. The non-acoustically-driven firing rate is shown as a function of the membrane potential for 17 neurons in Fig. 1B (6 other neurons were excluded from statistics either because their resting membrane potential might have had a direct current bias or their spike amplitude was not large enough to overshoot to positive voltage). Available data points over five membrane potentials in Fig. 1B were averaged and shown in Fig. 1C. The non-acoustically-driven firing rate was  $45.8 \pm 23.3$  Hz (mean  $\pm$  S.D.,  $n = 8$ ) at a membrane potential of  $-45$  mV,  $30.6 \pm 19.4$  Hz ( $n = 14$ ) at  $-50$  mV,  $18.0 \pm 12.9$  Hz ( $n = 14$ ) at  $-55$  mV, and significantly decreased to  $5.7 \pm 7.4$  Hz at  $-60$  mV and to  $0.7 \pm 1.5$  Hz ( $n = 10$ ) at  $-65$  mV (ANOVA,  $P < 0.001$ ). There was a large variation over different neurons at each membrane potential.

### 3.2. Membrane potential dependent auditory response

The driven activity also changed as a function of the resting membrane potential. Fig. 2 shows the responses of a neuron to acoustic stimulation at three different resting membrane potentials. The neuron fired at 6.5 spike/s, when the membrane potential was  $-55$  mV, and decreased to 0.8 spike/s at  $-63$  mV, and to null at  $-75$  mV. Some neurons showed a large after-hyperpolarization following the non-acoustically-driven spikes (Fig. 2) and others showed no after-hyperpolarization (Fig. 1).

The auditory responsive neuron in Fig. 2 responded to a repeated noise-burst stimulus, but not to pure tones (data not shown). The neuron showed a burst of 3 spikes when the resting membrane potential was  $-55$  mV, the number of spikes in the burst decreased to an average of 2.5 spikes at  $-63$  mV, and decreased further to  $<2$  spikes at  $-75$  mV. As it was becoming hyperpolarized, the neuron showed a longer response latency from 21.8 ms at  $-55$  mV, to 28.2 ms at  $-63$  mV and 32.1 ms at  $-75$  mV. The inter-spike-interval (ISI) of the auditory evoked spikes also increased from

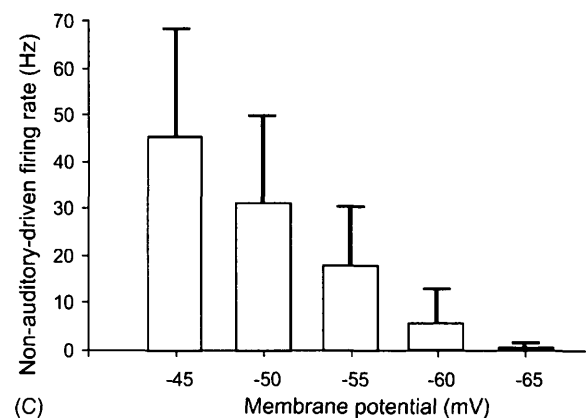
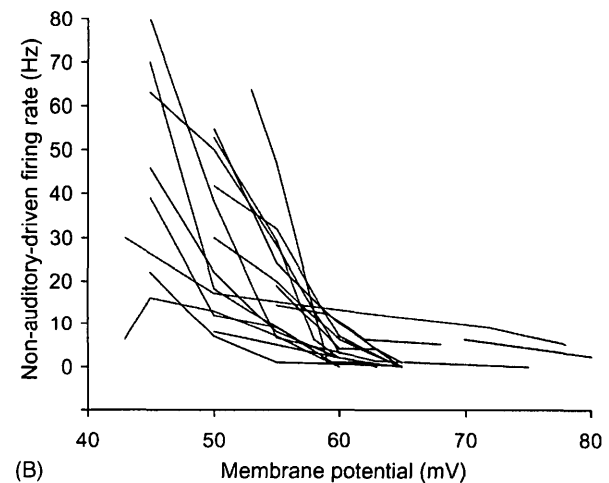
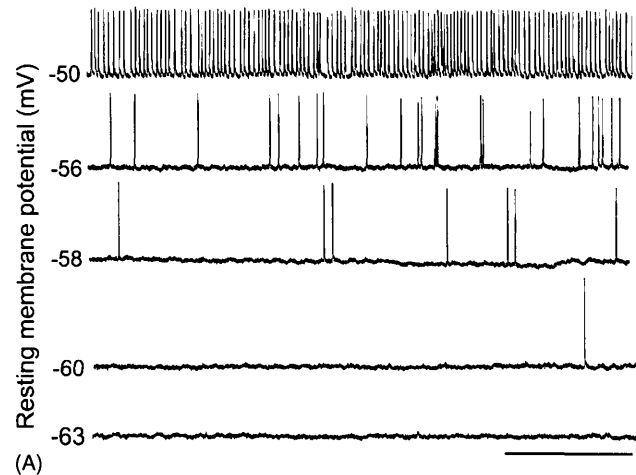


Fig. 1. Spontaneous firing as a function of resting membrane potential. (A) Spontaneous neuronal firing at varied resting membrane potentials. Recording was carried out during natural drifting of the resting membrane potential. Time scale: 1 s. (B) The relationships between the non-acoustically-driven firing rate and the resting membrane obtained from 17 typical neurons in the MGB. The membrane potential of some neurons was manipulated by injecting either negative or positive current into the neurons and is not specified in (C). (C) Averaged non-acoustically-driven firing rates at five sampled membrane potentials. Data were collected from the curves over the sampled membrane potential points in (B).

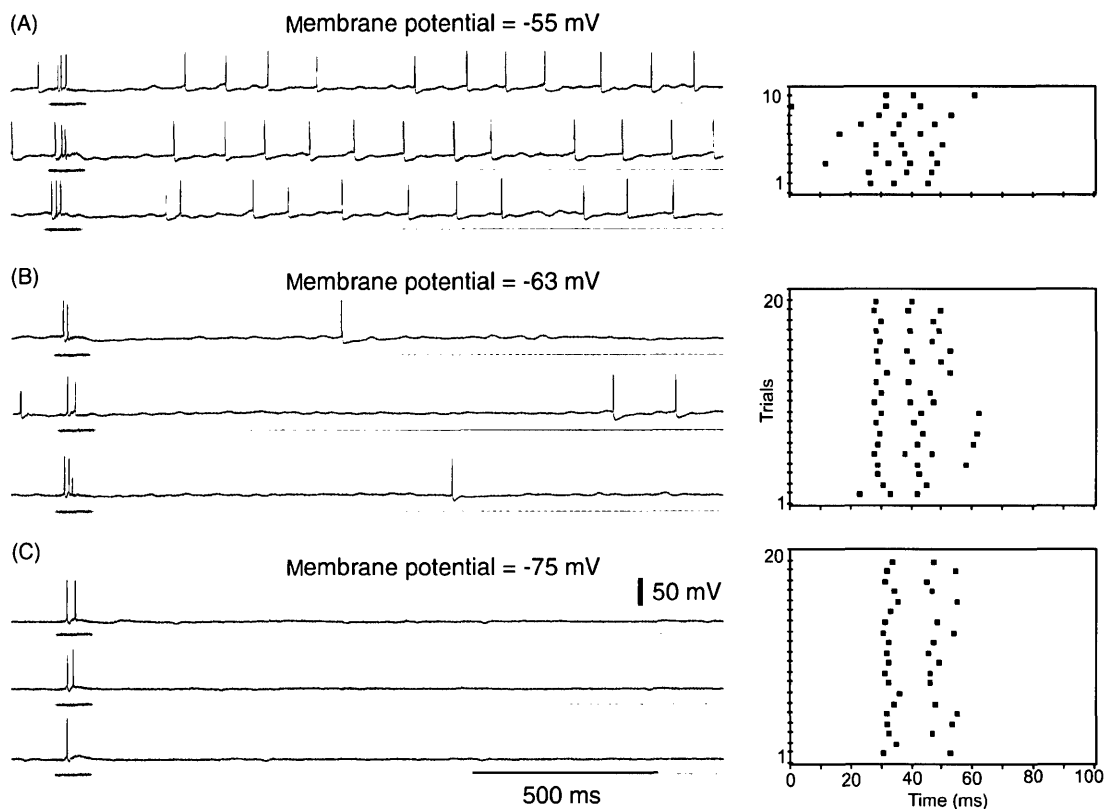


Fig. 2. Neuronal responses as a function of membrane potential. The left panel shows the intracellular traces of the neuronal responses to noise-burst stimuli of three trials of an MGB neuron at varied membrane potential: (A)  $-55$  mV; (B)  $-63$  mV; (C)  $-75$  mV. Stimuli are shown under each response trace. Scale bars of time and voltage in (C) apply to all. The right panel shows the raster displays of the first 100 ms of the neuronal responses to repeated noise-burst stimuli of 10 trials (A) or 20 trials (B and C). Time scale in (C) applies to all.

12.4 ms at  $-55$  mV to 13.1 ms at  $-63$  mV and to 17.1 ms at  $-75$  mV. The auditory responsiveness of the MGB neurons depended on the membrane potential in the range of  $-45$  to  $-75$  mV: the higher the membrane potential, the greater the responsiveness, and vice versa.

### 3.3. Frequency tuning characteristic

MGB neurons with short latency responses and located ventrally were frequency tuned. The neuron in Fig. 3 responded to acoustic stimuli of low frequencies better than those of high frequencies. It responded to 4 kHz with a train of three spikes and a short response latency of  $13.5 \pm 0.6$  ms and to 1 kHz with one to two spikes and a shortest latency of  $10.3 \pm 0.7$  ms. The neuron also responded to other frequencies, with 2–3 spikes to 6 kHz (latency:  $23.0 \pm 1.8$  ms), and 0–1 spikes to 15 kHz (latency: 21.5 ms). The response–frequency function of Fig. 3B showed the frequency tuning of the neuron, though the tuning was broad at 60 dB SPL. There was a trend that the neurons showed an increased first-spike latency when the frequency increased.

Note that the burst of the lower trace of 6 kHz had a much longer ISI than that of the response to 4 kHz, even though both fired the same number of spikes (3). The ISIs between the first and second spikes and between the second and third

spikes were 10.8 and 12.6 ms ( $n = 2$ ), respectively, for 6 kHz, while those for 4 kHz were  $4.0 \pm 0.3$  and  $9.3 \pm 1.6$  ms ( $n = 5$ ), respectively.

### 3.4. Two types of spike bursts

Compared with the frequently reported LTS bursts in the thalamus, the spike bursts in Figs. 2 and 3 had a much longer ISI and were based on a higher membrane potential. Fig. 4 shows a comparison between the two types of spike bursts. The spike trains in Fig. 4A were evoked when the membrane potential was hyperpolarized into  $< -85$  mV and were categorized as LTS bursts and those in Fig. 4B had a longer ISI and rose from a higher membrane potential of about  $-53$  mV. The ISIs between the first and second spikes and between the second and third spikes were sampled from 20 bursts for each neuron and are shown in Fig. 4C. The mean over first and second ISIs of the LTS bursts in Fig. 4C was  $6.7 \pm 2.4$  ms ( $n = 40$ ), which was significantly shorter than the mean ISI of the non-LTS bursts,  $11.6 \pm 6.0$  ms ( $n = 40$ ,  $P < 0.001$ ,  $t$ -test).

The mean of the second ISI of the LTS bursts ( $7.1 \pm 2.4$  ms) was significantly longer than that of the first ISI ( $5.9 \pm 1.2$  ms,  $n = 20$ ,  $P < 0.01$ , paired  $t$ -test). The mean of second ISI of the non-LTS bursts ( $13.1 \pm 7.0$  ms) was

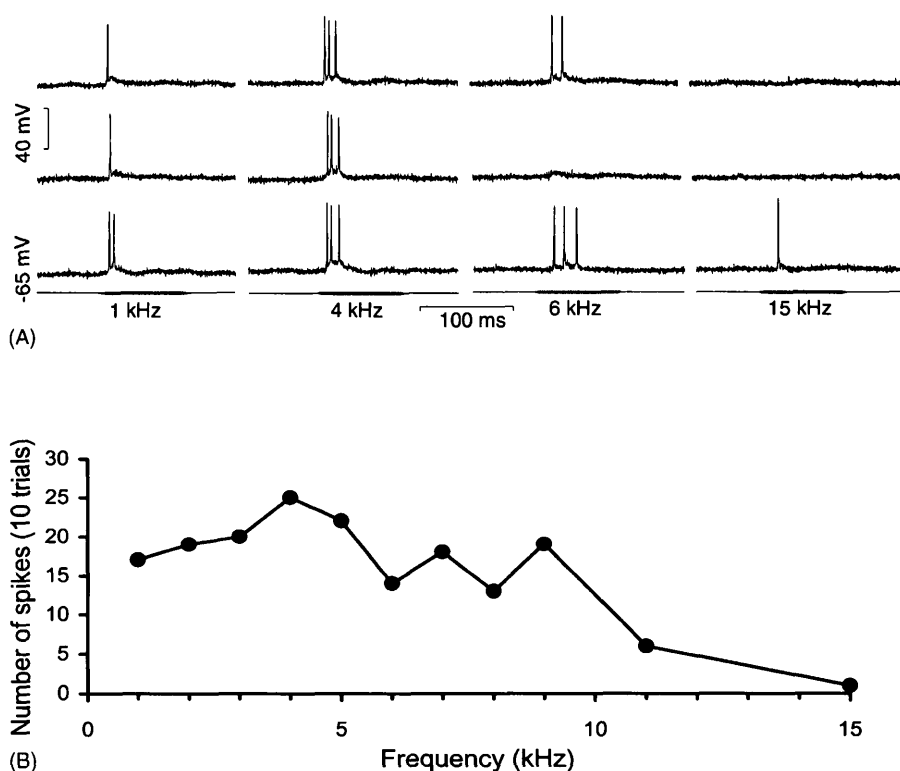


Fig. 3. Frequency tuning of a MGB neuron. (A) Neuronal responses to pure-tone stimuli of four different frequencies: 1, 4, 6, and 15 kHz. Three repeats, sampled from 10 repeats, are shown in the figure. Resting membrane potential was  $-65$  mV. Scale bars apply to all. (B) A response–frequency function at an intensity of 60 dB SPL and no current injection. The number of spikes was counted over 10 repeated pure-tone stimuli of various frequencies.

longer than that of the first ISI ( $10.1 \pm 4.6$  ms), but not statistically significant ( $n = 20$ ,  $P > 0.05$ ). The non-statistical significance might have resulted from the large deviation of the parameter.

## 4. Discussion

### 4.1. Non-acoustically-driven firing

The finding that the non-acoustically-driven firing rate depended on the membrane potential was not surprising. It is often reported that injection of a small positive current intracellularly which would depolarize the membrane potential causes an increase in the non-acoustically-driven firing rate (Smith and Populin, 2001; Sukov and Barth, 2001; Torterolo et al., 1995; White et al., 1994). The present study provided a quantitative assessment of the maximum non-acoustically-driven firing rate of the thalamic relay neurons and the relationship between the non-acoustically-driven firing rate and membrane potential.

### 4.2. Membrane potential-dependent auditory responses

Like the non-acoustically-driven firing rate, the auditory response also depended on the membrane potential, which was manipulated by injecting current into the thalamic neu-

rons. In the present study, we injected current into the thalamic neurons to manipulate the membrane potential. We found an increased response when the membrane potential was depolarized and a decreased response when the membrane potential was hyperpolarized.

Anatomically, the corticothalamic fibers terminate on the distal parts of the dendrites of relay neurons and have a cumulative effect on the neurons (Deschênes and Hu, 1990; McCormick and von Krosigk, 1992; Liu et al., 1995a,b; He, 1997). Extracellular studies triggered the speculation that the corticothalamic fibers change the responsiveness of thalamic neurons rather than directly evoking them to fire (He, 1997, 2001; He et al., 2002). The present result of membrane potential dependence of the responsiveness of the thalamic neurons would provide one basis for the mechanism of the corticothalamic modulation of thalamic neurons. The exact mechanism by which corticofugal fibers exert modulatory effects on thalamic relay neurons is being addressed currently in our laboratory with intracellular recording of the responses to an auditory stimulus while the corticofugal pathway is being directly manipulated.

### 4.3. Firing patterns

Burst responses have been frequently observed in the auditory thalamus and more often in the non-lemniscal MGB (Hu and Bourque, 1992; Strohmman et al., 1994; Hu, 1995;

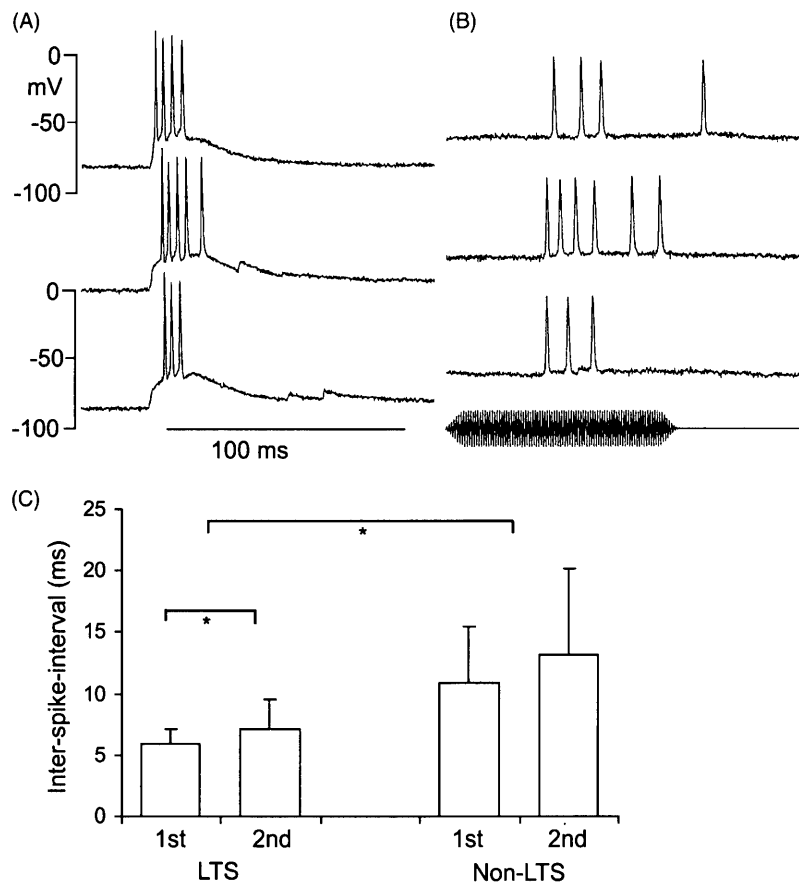


Fig. 4. Spike bursts at varied membrane potentials. (A) Non-acoustically-driven spike bursts at a hyperpolarized membrane potential of  $-85$  mV. (B) The neuron responded with a spike burst to pure-tone stimulus at a depolarized membrane potential of  $-53$  mV. (C) Mean inter-spike intervals (ISI) of two neurons were calculated over 20 bursts. The first ISI means the interval between the first and second spikes and second ISI means that between the second and third spikes. LTS: low-threshold calcium spike. (\*)  $P < 0.01$ .

He and Hu, 2002). A commonly cited mechanism of thalamic neuronal bursting relies on voltage-dependent activation of an LTS or LTS burst (Jahnsen and Llinás, 1984; Steriade and Llinás, 1988; Deschênes and Hu, 1990; McCormick and Feeseer, 1990; Hu, 1995; Turner et al., 1997). The present result in Fig. 4A was categorized as LTS bursts (see also Xiong et al., 2001). The LTS bursts in the present study showed a shorter first ISI than the second ISI in agreement with previous findings (Fig. 4, He and Hu, 2002; Hu and Bourque, 1992; Steriade et al., 1993; Hu, 1995). The LTS bursts evoked by natural sound stimulation showed a relatively longer ISI than those recorded in the slice and evoked by current injection (3–4 ms, He and Hu, 2002 and 4–7 ms, Fig. 4 of the present study in vivo versus 1–3 ms for the first and second ISI in vitro, Turner et al., 1997).

Among the present results, the burst responses of Figs. 2, 3 and 4B were non-LTS and showed more spikes in the burst when the resting membrane potential was higher instead of lower. In general, the non-LTS bursts in Figs. 2, 3 and 4B showed longer ISIs than that of the LTS bursts (Fig. 4C). The characteristics of spike bursts in Fig. 4B are similar to those recorded from relay neurons in the ventrobasal thalamus (Fig. 10 of Turner et al., 1997). It was

suggested that burst firing may have a stronger impact on the cortex (Swadlow and Gusev, 2001). We know that neurons in the lemniscal and non-lemniscal MGB are involved in different signal processing providing a dual-pathway through the MGB (Merzenich et al., 1982; Imig and Morel, 1983; Jones, 1985; LeDoux et al., 1990; Edeline and Weinberger, 1992; Hu, 1995; Rauschecker et al., 1997; Kosaki et al., 1997; LeDoux, 2000; He, 2001; He and Hu, 2002). It would be interesting to see whether there is any difference in spike burst generation in the lemniscal and non-lemniscal MGB.

The inter-spike-interval of burst responses changed with the frequency of a pure-tone stimulus, even though the number of spikes could be similar. This result provides us with evidence supporting the theory that neurons code sensory information not only with the spike number, but also with the temporal structure of the spikes/spike-burst (Middlebrooks et al., 1994; He et al., 1997, 2002). The temporal structure and the rate of neuronal responses are dependent on each other. With intracellular recording, the temporal features of the spikes and post-synaptic potentials should provide us valuable information to evaluate the temporal coding theory.

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