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·Original Article·

Local neuronal circuits that may shape the discharge patterns of inferior collicular neurons

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ABSTRACT

The discharge patterns of neurons in auditory centers encode information about sounds. However, few studies have focused on the synaptic mechanisms underlying the shaping of discharge patterns using intracellular recording techniques. Here, we investigated the discharge patterns of inferior collicular (IC) neurons using intracellular recordings to further elucidate the mechanisms underlying the shaping of discharge patterns. Under *in vivo* intracellular recording conditions, recordings were obtained from 66 IC neurons in 18 healthy adult mice (*Mus musculus*, Km) under free field-stimulation. Fifty-eight of these neurons fired bursts of action potentials (APs) to auditory stimuli and the remaining eight just generated local responses such as excitatory (n = 4) or inhibitory (n = 4) postsynaptic potentials. Based on the APs and subthreshold responses, the discharge patterns were classified into seven types: phasic (24/58, 41.4%), phasic burst (8/58,13.8%), pauser (4/58, 6.9%), phasic-pauser (1/58, 1.7%), chopper (2/58, 3.4%), primary-like tonic (14/58, 24.1%) and sound-induced inhibitory (5/58,8.6%). We concluded that (1) IC neurons exhibit at least seven distinct discharge patterns; (2) inhibition participates in shaping the discharge pattern of most IC neurons and plays a role in sculpting the pattern, except for the primary-like tonic pattern which was not shaped by inhibition; and (3) local neural circuits are the likely structural basis that shapes the discharge patterns of IC neurons and can be formed either in the IC or in lower-level auditory structures.

Keywords: inferior collicular neuron; discharge pattern; synaptic mechanism; local neuronal circuit; *in vivo* intracellular recording

INTRODUCTION

The discharge pattern of a central auditory neuron is considered to be a basic characteristic of that neuron[1] and most of the patterns have been obtained by extracellular recording. Therefore, the types of patterns have generally been based on their post-stimulus time histograms (PSTHs)[1-7]. With the wide use of *in vivo* intracellular recording[8-10] and whole-cell patch clamping in brain slices[11-17], the relationship between the discharge pattern and the properties of the cell membrane of a neuron is gradually being taken into account.

The discharge pattern of a neuron in an auditory center can encode information such as sound duration[7,18], the onset and offset of an auditory signal[19-21], the pattern of an auditory stimulus[22,23], an interaural intensity difference[24,25], a conditioned task[26] and auditory perception[27]. Thus, investigating the mechanisms underlying the shaping of the discharge patterns of central auditory neurons is of great importance. Since each central auditory

neuron is located within a local neuronal circuit (LNC), in which neurons form a functional unit that independently integrates information at the local level, its discharge or response pattern and biological function are affected by other local neurons. Iontophoresis of blockers of inhibitory neurotransmitter receptors[28-30] and injection of depolarizing or hyperpolarizing current[13-15,31] are widely used to investigate the formation of discharge patterns and the results show that neuronal inhibition plays an important role in shaping the patterns in central auditory neurons. However, current-injection differs from real synaptic input in LNCs, so the responses to auditory stimuli under *in vivo* recording conditions are quite different from those to current-injection under *in vitro* recording conditions[13,15]. Therefore, the results obtained by current-injection cannot completely explain the mechanisms underlying the shaping of discharge patterns in neurons receiving auditory stimulation, so further studies are needed.

Because only action potentials (APs) can be detected with extracellular recording, the variations in the local membrane potential before and/or after an AP as well as the spatial and temporal summation of excitatory and inhibitory inputs are largely missed. Although intracellular recording and whole-cell patch clamping are efficient methods for further studying the mechanisms that shape discharge patterns, few studies have done this. In the present study, we investigated the discharge patterns of inferior collicular (IC) neurons in mice using *in vivo* intracellular recording under free-field stimulation and presented hypothetical models of LNCs that shape these patterns.

MATERIALS AND METHODS

Animal Preparation

Eighteen healthy adult (2–3 months) mice were purchased from the Center for Disease Control and Prevention of Hubei Province, China. The surgical procedures for recording were basically the same as described in previous studies[32]. After surgery was performed on each anesthetized mouse (Nembutal, 60–90 mg/kg)[23,32], the mouse with a flat-head nail glued to its head was placed in a sound-proof room (temperature 28–30°C). The nail was fixed onto a stainless steel rod to immobilize the head, and the physiological condition (respiration rate) of anesthetized animal was monitored throughout the recording session. The experiments were approved by the Institutional Animal Care and Use Committee of Central China Normal University, Wuhan, China.

Acoustic Stimulation and Recording of Neuronal Responses

Tone-bursts were produced by a neurophysiology workstation (TDT 3, Tucker-Davis Technologies, FL) and adjusted with TDT software (OpenEx). Tone-bursts of different durations (40, 120, 200 and 300 ms) and 5-ms rise-decay times were delivered (once per second) at the best frequency (BF) and 20 dB above the minimum threshold (MT) of each neuron, and passed to the mouse through a loudspeaker (ED 1, Tucker-Davis Technologies) located 20 cm from the ear contralateral to the recording position. The loudspeaker was calibrated with a B&K calibration system (4939, 2610, B&K, Narum, Denmark).

Before recording, a single glass capillary (outer diameter,1.5 mm; thick-walled, with a filament in the lumen) was pulled into a microelectrode (tip diameter <1 μm) with a microelectrode puller (PULL-100, WPI, Sarasota, FL). The microelectrode was filled with 1 mol/L tri-potassium citrate (impedance, 23–104 MΩ). A hole (200–500 μm in diameter) was made in the skull above the IC, and the dura was pricked with a needle for orthogonal insertion of the electrode to record neuronal responses to tone-bursts. A silver wire in the temporal muscle was used as the indifferent electrode. The depth from the surface of the IC of each recorded neuron was obtained from the remote controller of the microelectrode drive (SM-21, Narishige, Japan). When the surface of the IC was reached, the electrode resistance was shown. And when the electrode penetrated an IC neuron, a negative membrane potential (resting potential) was detected, and then all the responses of the neuron were led to an amplifier (Due 773, WPI; Axon Axopatch 200B, AXON, NY) and a computer (Pentium 4 Lenovo, China) with software (AxoScope; Axon Instruments, NY) for amplification and data acquisition. A cell can be hold from 8 min to 1 h. The unidirectional APs (along with excitatory and inhibitory postsynaptic potentials) evoked by 10 tone-bursts were transformed into post-stimulus-time histograms (PSTHs). The discharge pattern of a neuron was analyzed based on its APs, the PSTH, and the postsynaptic potentials.

RESULTS

Intracellular recording was obtained from 66 IC neurons *in vivo* under free-field stimulation conditions. The range of recording depths was 151–1871 μm (792.9 ± 354.1), that of BFs was 8–38 kHz (13.9 ± 4.7), and of resting potential was −57 to −15 mV (−19.7 ± 12.1). Fifty-eight of these neurons responded with bursts of APs to the stimulus, and the remaining eight only generated excitatory postsynaptic potentials (EPSPs; n = 4) and inhibitory postsynaptic potentials (IPSPs; n = 4). In this study, we focused mainly on the neurons that generated APs to auditory stimulation. Discharge patterns were determined from APs evoked by a single presentation and PSTHs were constructed from APs responding to 10 presentations. Based on the AP bursting pattern and subthreshold responses, the discharge patterns were classified into seven types: phasic, phasic-burst, pauser, phasic-pauser, chopper, primary-like tonic, and sound-induced inhibitory.

Twenty-four neurons (24/58, 41.4%) were typical phasic neurons that generated onset responses (1–3 APs) to a BF sound of 80 dB SPL for 120 ms (Fig. 1A, B). Although the patterns of the PSTHs of the two representative neurons were the same (Fig. 1.C, D), their membrane potential responses were different. In one neuron, the AP was followed by a large IPSP (Fig. 1A) while the AP of the the other had no IPSP (Fig. 1B). The different membrane potential changes suggested that different LNCs probably contributed to the responses of these two phasic neurons. Besides, eight neurons (8/58, 13.8%) generated 3–5 APs in response to a single BF presentation of 80 dB SPL for 120 ms. According to their membrane potential changes and PSTHs, they were classified as having a phasic-burst pattern (Fig. 2A, B).

Another four of the 58 IC neurons (6.9%) displayed the pauser pattern. These neurons generated an onset

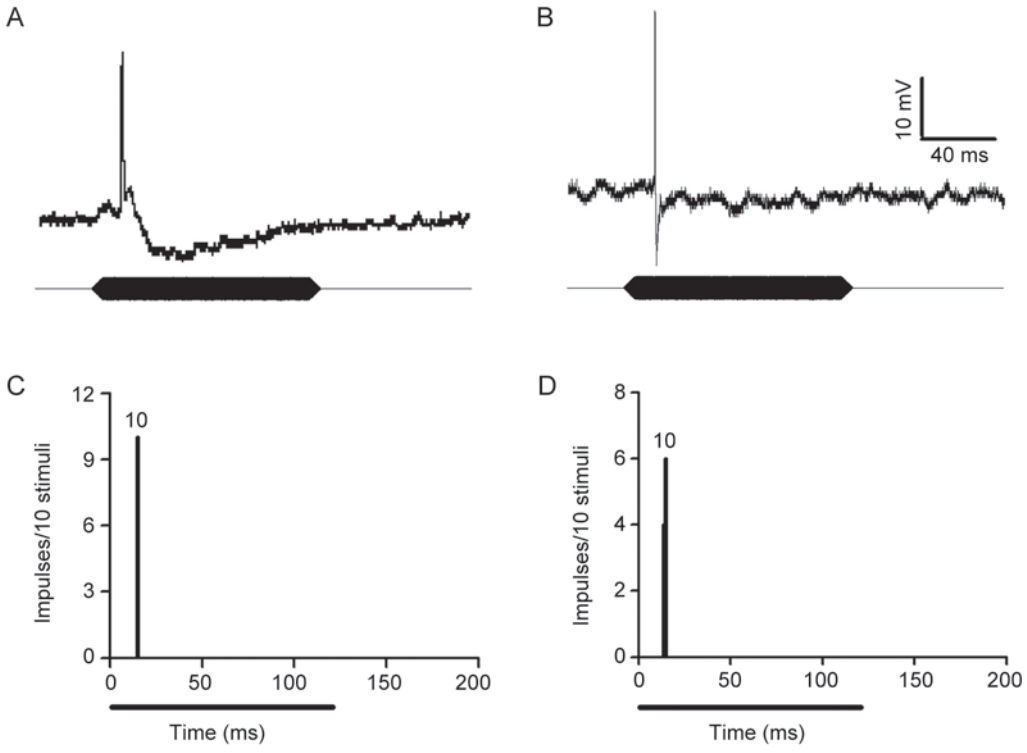

Fig. 1. Two representative IC neurons with the phasic pattern. A and B show their responses to a BF stimulus of 80 dB SPL for 120 ms. C and D show the PSTH of the corresponding neuron. The number of APs is shown above each PSTH. The recording depth, BF, and resting potential of these neurons were 556 μm, 24 kHz, and –21 mV for A, and 1095 μm, 23 kHz, and –19 mV for B. The symbols under the traces (A and B) and the bars under the abscissas (C and D) represent the stimuli.

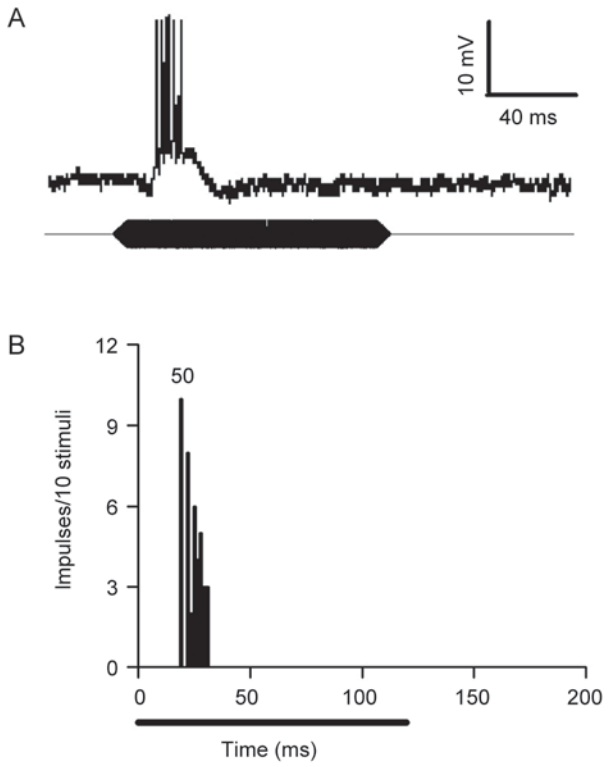

Fig. 2. A representative IC neuron with the phasic burst pattern. A and B show the response to a single BF sound presentation of 80 dB SPL for 120 ms and the corresponding PSTH. The number of APs is shown above the PSTH. For this neuron, the recording depth was 715 μm, the BF was 11 kHz, and the resting potential was –43 mV. The symbol under trace A and the bar under abscissa in B represent sound stimuli.

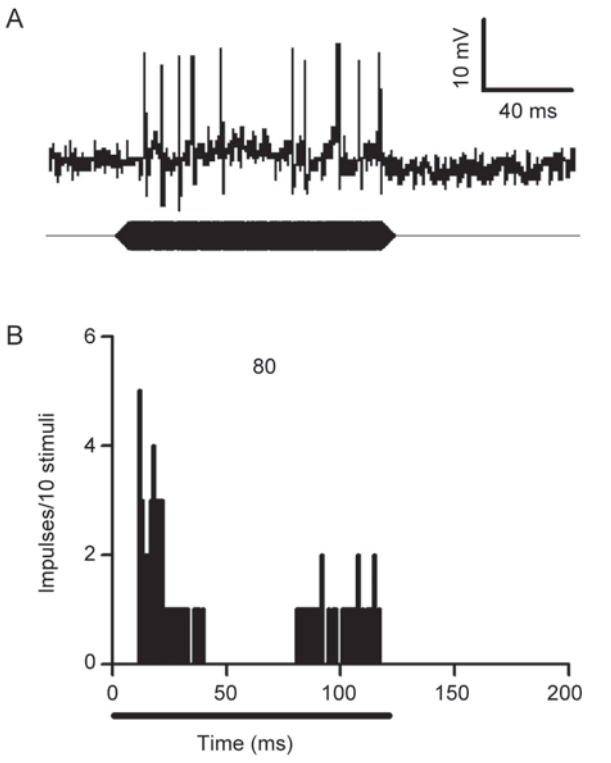

Fig. 3. A representative IC neuron with the pauser pattern. A and B show the response to a single BF sound of 80 dB SPL for 120 ms and the PSTH. The number of APs is shown above the PSTH. For this neuron, the recording depth was 1262 μm, the BF was 11 kHz, and the resting potential was –26 mV. The symbol under trace A and bar under the abscissa in B represent the stimulus.

response to a stimulus and then generated a successive response again after a pause (Fig. 3A, B). We also found one IC neuron with a special discharge pattern called a phasic-pauser (1/58, 1.7%) (Fig. 4). This neuron's discharge pattern to BF sound stimuli of 80 dB SPL for 120 ms yielded a similar phasic pattern (Fig. 4A, B, E, F) while the discharge in response to stimuli lasting 200 and 300 ms elicited the pauser pattern (Fig. 4C, D, G, H).

Two neurons (2/58, 3.4%) discharged in the chopper pattern (Fig. 5). The membrane potential response and PSTH showed regular peaks and notches of AP firing (Fig. 5A, B). Another fourteen neurons (14/58, 24.1%) were classified as having a primary-like tonic pattern in which the burst was sustained during the entire duration of the stimulus with a relatively weak phasic component at stimulus onset (Fig. 6).

In addition, five neurons (5/58, 8.6%) exhibited spontaneous activity or a background discharge during intracellular recording (Fig. 7). However, when a stimulus was presented, an IPSP occurred and the spontaneous activity was terminated. We defined these neurons as having the sound-induced inhibitory pattern since the stimulus evoked inhibition in both the membrane potential response (Fig. 7C) and the PSTH (Fig. 7D).

DISCUSSION

In the mammalian auditory pathway, the IC receives and integrates excitatory and inhibitory inputs from many lower nuclei. For example, when one ear is stimulated, the excitatory inputs to the IC can come from the contralateral cochlear nucleus, the contralateral lateral superior olive,

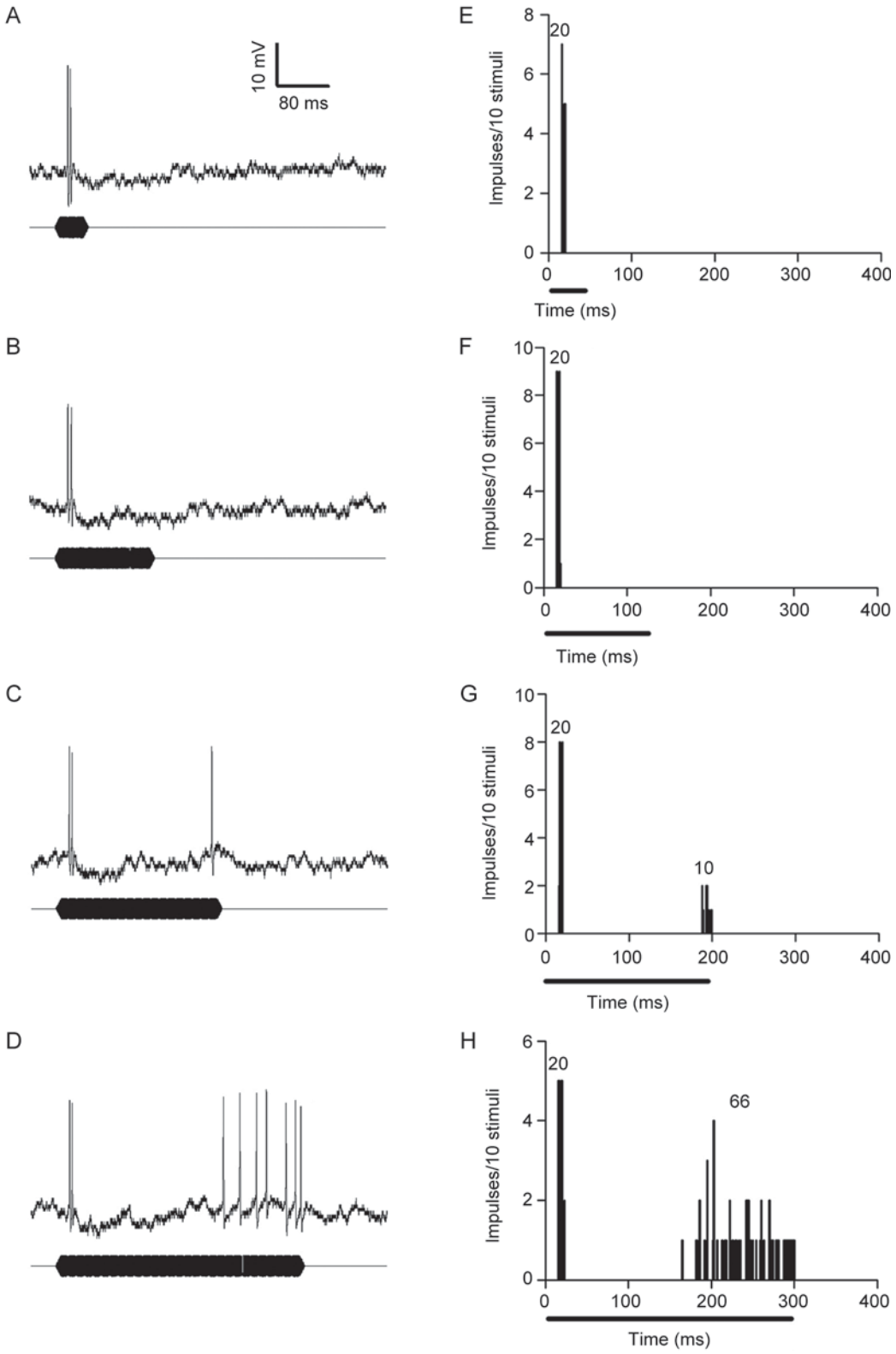

Fig. 4. An IC neuron with the phasic-pauser pattern. A–D show the responses to BF stimulation at 80 dB SPL for 40, 120, 200, and 300 ms. E–H show the PSTHs. The number of APs is shown above each PSTH. For this neuron, the recording depth was 854 μm, the BF was 8 kHz, and the resting potential was –16 mV. The symbols under traces A–D and the bars under the abscissas in E–H represent the stimuli.

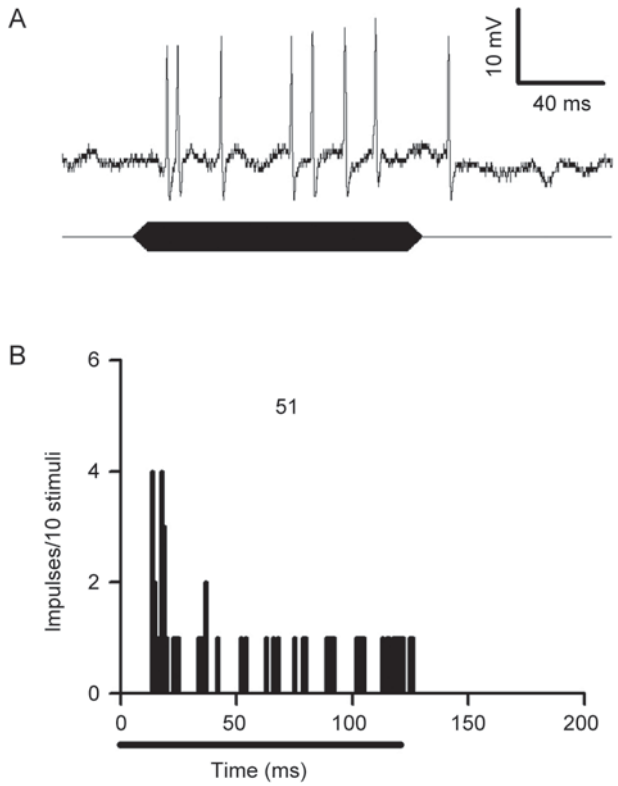

Fig. 5. An IC neuron with the chopper pattern. A and B show the response to a single BF stimulus at 80 dB SPL for 120 ms. The number of APs is shown above the PSTH. The recording depth was 522 μm, the BF was 13 kHz, and the resting potential was –22 mV. The symbol under trace A and the bar under the abscissa in B represent the stimulus.

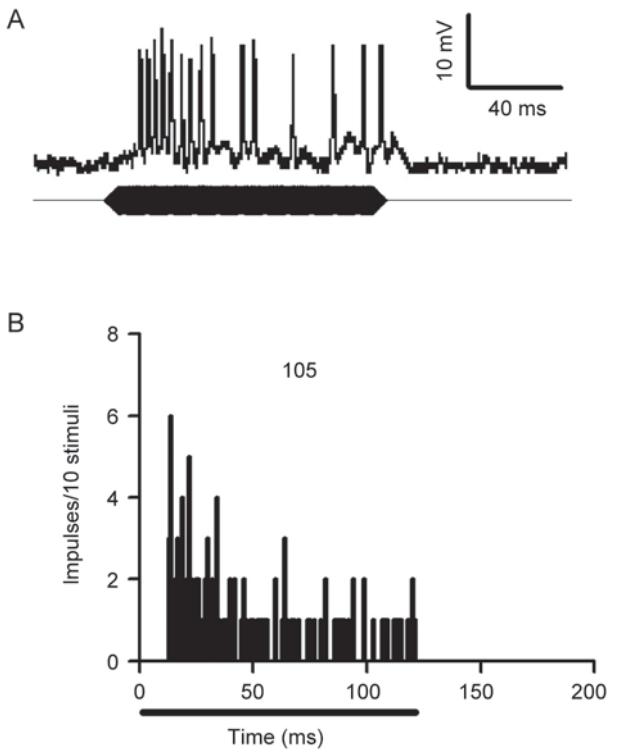

Fig. 6. A representative IC neuron with the primary-like tonic pattern. A and B show the response to a single BF stimulus at 80 dB SPL for 120 ms and the PSTH. The number of APs is shown above the PSTH. The recording depth was 785 μm, the BF was 12 kHz, and the resting potential was –20 mV. The symbol under trace A and bar under the abscissa in B represent the stimulus.

and the ipsilateral medial superior olive, while inhibitory inputs can come from the ventral and dorsal nuclei of the lateral lemniscus[33-35]. Besides ascending inputs from lower centers, IC neurons also receive descending inputs from the auditory cortex and intrinsic inputs from local collaterals[36]. So, discharge patterns in the IC can be modulated by the interplay of excitatory and inhibitory inputs.

Many IC neurons receive inputs from binaural sources and also receive monaural inputs that may participate in binaural interaction[36], so binaural interaction may play important roles in shaping the discharge patterns of IC neurons. Nasimi and Rees have reported that when an ipsilateral tone is added, the sustained rate of firing in some IC neurons decreases and a pause appears in the PSTH[25]. They also noted that, when comparing monaural and binaural PSTHs, the pause in the pauser units became deeper or wider with binaural stimulation[25]. Because most neurons in the IC are excited by contralateral stimulation, such a pause can be attributed to ipsilateral inhibition.

Since most of the discharge patterns of IC neurons described previously were based on extracellular recordings[1,4,7,16,37,38], many of the details of the patterns could not be seen. In the present study, we examined the discharge patterns of IC neurons by intracellular recording *in vivo* under free-field stimulation and obtained seven types: phasic, phasic-burst, pauser, phasic-pauser, chopper, primary-like tonic, and sound-induced inhibitory. Based on the membrane potential changes induced by sound stimulation, we suggested models of LNCs shaping

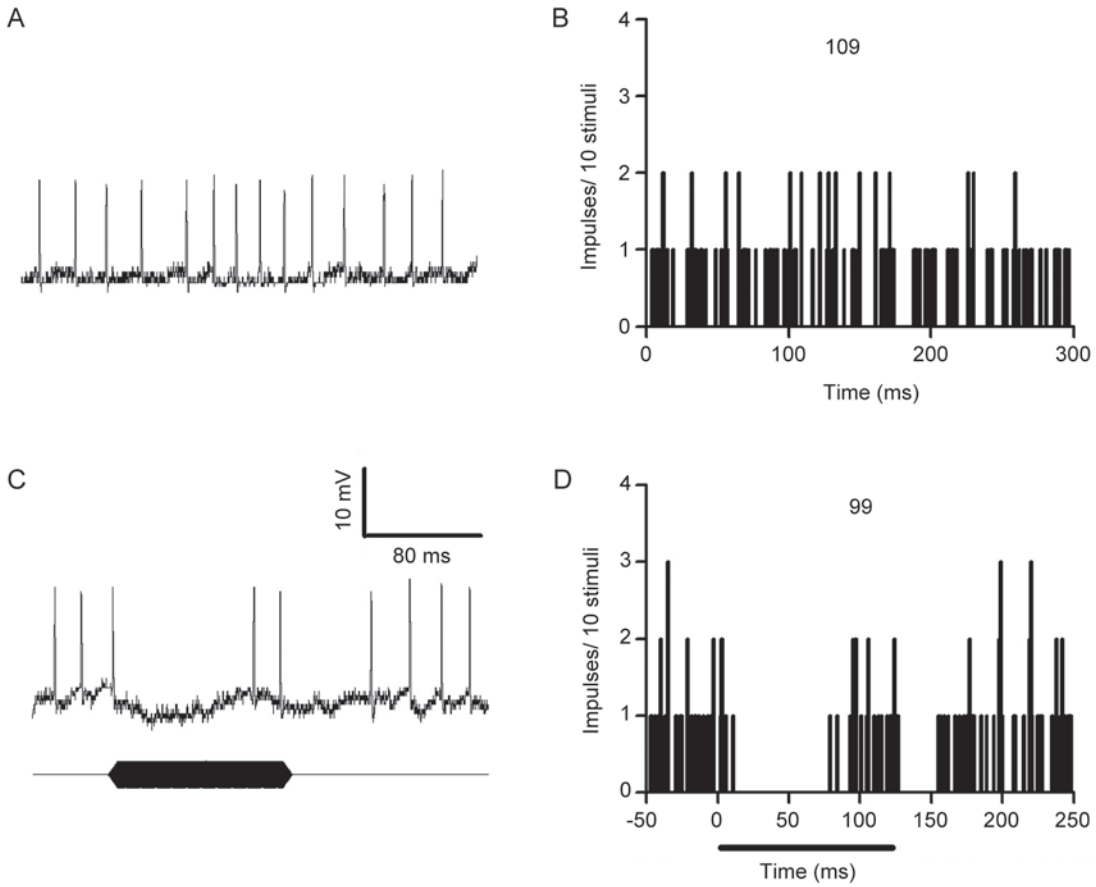

Fig. 7. A representative IC neuron with the sound-induced inhibitory pattern. A and B show the spontaneous activity and its PSTH. C and D show the response to a single BF stimulus at 80 dB SPL for 120 ms and the PSTH for 10 repetitions. The number of APs is shown above each PSTH. The recording depth was 577 μm, the BF was 12 kHz, and the resting potential was −23 mV. The symbol under trace C and the bar under the abscissa in D represent the stimulus.

the seven patterns.

LNC of the Phasic Pattern

The formation of the LNC shaping the phasic pattern was likely in the IC for most phasic neurons and in auditory structures below the IC (sub-IC) for a few of them. In the example in Fig. 1A, AP firing was abruptly ended through strong inhibition generated by an inhibitory interneuron; it was followed by an IPSP. As such, the LNC shaping the phasic pattern in this case was composed of an excitatory and one inhibitory interneuron, perhaps in the IC (Fig. 8A-1). On the other hand, the LNC shaping the phasic pattern shown in Fig. 1B was composed of two excitatory and an inhibitory interneuron, perhaps in a sub-IC auditory structure (Fig. 8A-2) because there was no evident inhibitory input in the trace and the brief excitatory input originated mainly in the periphery and the auditory nuclei in the lower brainstem[1]. Previous studies have shown that phasic neurons occur widely in the cochlear nucleus (CN), the ventral nuclei of the lateral lemniscus (VNLL) and other auditory nuclei in the lower brainstem below the IC[39-43]. A morphological study with a neuronal tracer also supports the idea that the phasic pattern of some IC neurons is formed in sub-IC auditory structures, because brief excitatory inputs originating in the CN are transmitted to the IC through the fast disynaptic pathway of the VNLL, which projects directly to the IC[44]. In addition, neuropharmacological studies demonstrate that during application of antagonists of GABAergic and glycinergic receptors, the phasic pattern of small IC neurons does

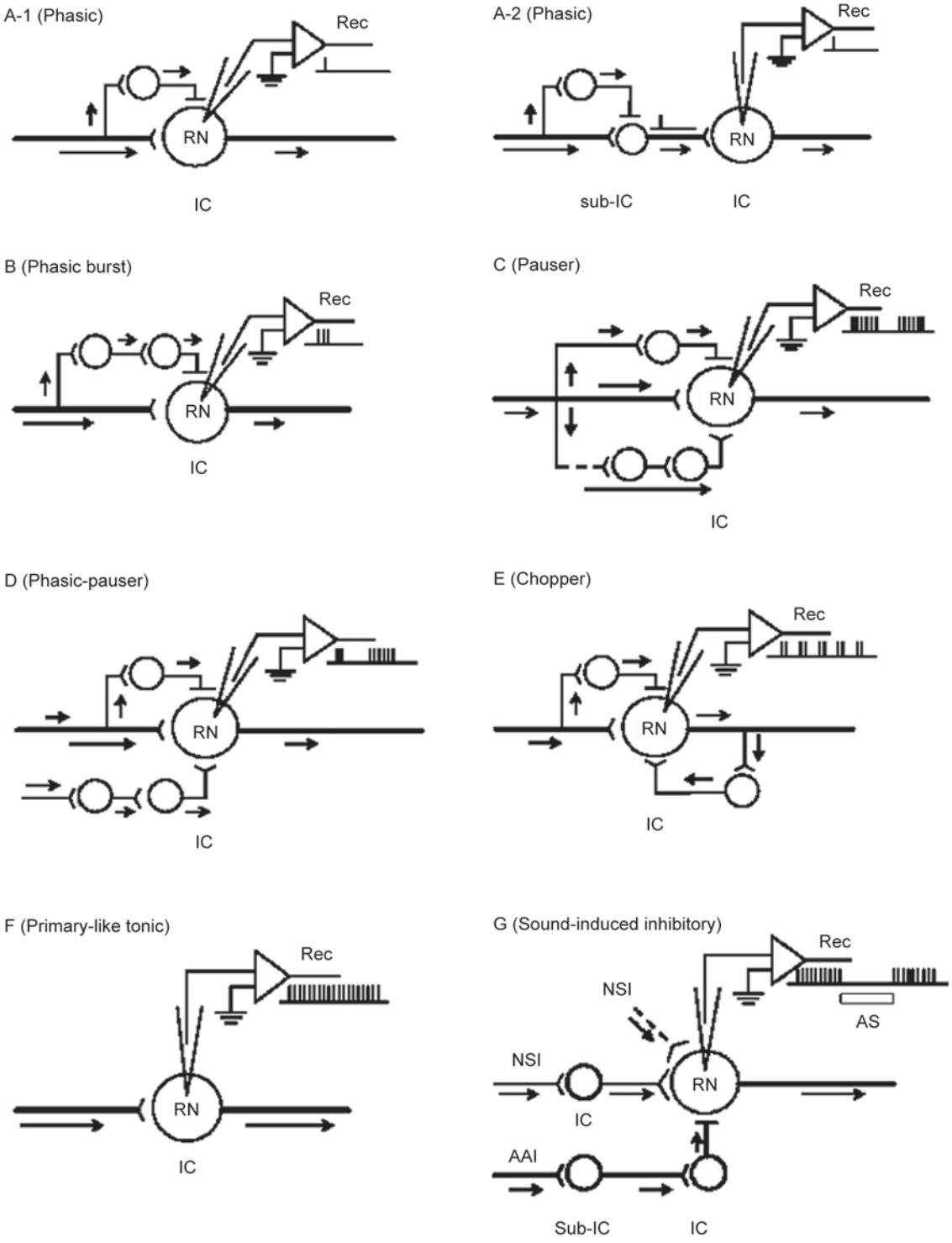

Fig. 8. Models of local neuronal circuits shaping the seven discharge patterns: phasic (A-1, A-2), phasic-burst (B), pauser (C), phasic-pauser (D), chopper (E), primary-like tonic (F) and sound-induced inhibitory (G), based on the membrane potential changes induced by an auditory stimulus. AAI: ascending auditory input; AS: acoustic stimulation; IC: inferior collicular; NSI: nonspecific input; Rec: recording; RN: recorded neuron; →: direction of excitatory conduction; ≺: excitatory synapse; ┤: inhibitory synapse.

not change, but the firing rates of >90% of IC neurons with a phasic pattern increase and the phasic pattern is transformed into a tonic or a chopper pattern[6,38]. These results imply that although inhibition in the IC does not participate in shaping the discharge patterns of a few IC neurons, the phasic pattern of most IC neurons is shaped by inhibitory synaptic input in the IC, which quickly terminates AP firing[45]. In summary, central auditory neurons with the phasic pattern play an important role in detecting the onset of a sound signal, coding a temporal signal and showing a phase-locked response to the stimulus, but do not participate in coding stimulus duration and amplitude[46].

LNC of the Phasic-burst Pattern

The LNC of the phasic-burst pattern might be composed of a recorded neuron, an excitatory and a few inhibitory interneurons, similar to that of phasic neurons, and is probably formed in the IC (Fig. 8B). However the number of interneurons was greater than that of the phasic neurons (Fig. 8B *vs* Fig. 8A-1), such that the duration of AP firing of the phasic burst neuron was slightly longer with the summation of synaptic delays. When bicuculline is applied to extracellularly-recorded neurons to block GABA receptors, 45.2% of neurons with a phasic-burst pattern are transformed into tonic or sustained neurons[6]. In addition, K^+ currents activated by current injection[46] and cation current (I_h) activated by hyperpolarization of the neuronal membrane[47] also participate in shaping the temporal discharge pattern of some onset neurons. As described above, the onset response of a neuron may be co-determined by several factors such as excitatory and inhibitory synaptic currents activated by an auditory stimulus, the intrinsic properties of the neuronal membrane, and voltage-sensitive ion channels. Because phasic-burst neurons typically respond at the onset, like phasic neurons, they may play similar roles in auditory signal processing.

LNC of the Pauser Pattern

We found four neurons with the pauser pattern (Fig. 3A, B), for which the LNC was likely composed of an inhibitory synaptic input and an excitatory multi-synaptic input from two branches of the same afferent projection (Fig. 8C). The inhibitory input shaped the first part of the AP firing while the excitatory input shaped the successive part after a short pause. Therefore, the pauser pattern is actually the result of interaction between excitatory and inhibitory synaptic inputs such that 69% of pauser neurons are transformed into other types of discharge patterns during bicuculline application[38,46,48]. The pauser neuron might be used to encode the interval between excitatory and inhibitory inputs.

LNC of the Phasic-pauser Pattern

The phasic-pauser neuron was specific, because the discharge pattern changed from phasic to pauser when the stimulus duration was >200 ms (Fig. 4). Based on the long duration-preference of this neuron, we hypothesized that the LNC shaping this pattern may be composed of two parts. One is afferent collateral inhibition which shapes the phasic response to stimuli of <200 ms, while the other is multi-synaptic afferent excitation to the recorded after a long latency, or multi-synaptic excitatory input from specific duration-preferring/sensitive neurons in the sub-IC (Fig. 8D). Therefore, the phasic-pauser neuron likely plays a role in recognizing the onset of an auditory signal with a specific duration.

LNC of the Chopper Pattern

The AP firing of IC neurons with the chopper pattern consisted of a series of regular peaks and notches (Fig. 5). We propose that the LNC shaping this pattern is mainly composed of two microcircuits. One inhibitory input from a branch of the afferent projection to the recorded neuron determined the duration of each AP burst. The other excitatory synaptic input from a recurrent branch of the efferent projection of the recorded neuron elicited a short train of APs (Fig. 8E). When the membrane is continuously depolarized, regular chopper-like AP firing is elicited[49]. In addition, the discontinuous spatial and temporal summation induced by convergent excitatory and inhibitory synaptic inputs may also be one of the reasons[50]. Therefore, chopper neurons may be involved in complex auditory signal processing.

LNC of the Primary-like Tonic Pattern

IC neurons with the primary-like tonic pattern generally showed slow adaption to continuous stimulation of long duration (Fig. 6). The responses of these neurons were probably not modulated by inhibition through the

ascending auditory pathway, because they did not have IPSPs. Therefore we suggest that there are no inhibitory interneurons in the LNC shaping the primary-like tonic pattern (Fig. 8F). Previous studies have demonstrated that direct excitatory inputs from the CN[2] always maintain sustained firing when ascending to the IC[2,7,20,39-41,51,52]. Therefore, the neurons with primary-like tonic pattern may have a strong capacity to encode the duration of an auditory signal[1,7,46].

LNC of the Sound-induced Inhibitory Pattern

We also found five IC neurons with spontaneous activity (Fig 7A, B), which was inhibited by auditory stimulation (Fig. 7C, D). A previous study[2] showed that spontaneous activity originates from the ventral CN projection to the IC while others showed it may originate from corticofugal and central non-auditory inputs, and some neurons fire spontaneously even without synaptic transmission[53-55]. The spontaneous activity of central auditory neurons may play a role in continuing excitation to increase the signal-to-noise ratio[1]. In addition, we speculate that spontaneous activity may also be involved in maintaining the excitability or an alert state in the central auditory system and the diversity of auditory functions. The LNC shaping the sound-induced inhibitory pattern (Fig. 8G) is composed of an excitatory afferent projection originating from the IC or non-auditory structures and multi-synaptic inhibition from sub-IC auditory structures. They form a convergent excitatory and an ascending inhibitory pathway. The excitatory inputs in the LNC produce the spontaneous activity while inhibitory input is activated by an auditory stimulus, thereby producing a sound-induced inhibition. Therefore, the sound-induced inhibitory pattern may regulate the signal-to-noise ratio and elicit auditory attention.

Based these intracellular recordings from IC neurons, we conclude that (1) IC neurons exhibit at least seven discharge patterns; (2) neuronal inhibition participates in shaping the patterns of most IC neurons and plays a role in sculpting the pattern. The primary-like tonic neurons (24.1%) are an exception in that inhibition does not shape the pattern; and (3) the various LNCs are the possible structural basis for shaping the discharge patterns of IC neurons and can be formed either in the IC or in sub-IC auditory structures.

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