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SUPPRESSION OF SPONTANEOUS FIRING IN INFERIOR COLLICULUS NEURONS DURING SOUND PROCESSING

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Abstract—Spontaneous activity is a well-known neural phenomenon that occurs throughout the brain and is essential for normal development of auditory circuits and for processing of sounds. Spontaneous activity could interfere with sound processing by reducing the signal-to-noise ratio. Multiple studies have reported that spontaneous activity in auditory neurons can be suppressed by sound stimuli. The goal of this study was to determine the stimulus conditions that cause this suppression and to identify possible underlying mechanisms. Experiments were conducted in the inferior colliculus (IC) of awake little brown bats using extracellular and intracellular recording techniques. The majority of IC neurons (82%) fired spontaneously, with a median spontaneous firing rate of 6 spikes/s. After offset of a 4 ms sound, more than half of these neurons exhibited suppression of spontaneous firing that lasted hundreds of milliseconds. The duration of suppression increased with sound level. Intracellular recordings showed that a short (<50 ms) membrane hyperpolarization was often present during the beginning of suppression, but it was never observed during the remainder of the suppression. Beyond the initial 50 ms period, the absence of significant changes in input resistance during suppression suggests that suppression is presynaptic in origin. Namely, it may occur on presynaptic terminals and/or elsewhere on presynaptic neurons. Suppression of spontaneous firing may serve as a mechanism for enhancing signal-to-noise ratios during signal processing. Published by Elsevier Ltd on behalf of IBRO.

Key words: IPSP, intracellular recording, signal-to-noise ratio, awake animal, bat, frequency modulated sweep.

Neurons throughout various brain structures, including those of sensory systems, have been shown to fire in the absence of overt external stimuli. Spontaneous firing is an important and necessary contributor to normal brain function. Research in this area has grown (Walsh and McGee, 1987; Gummer and Mark, 1994; Hermann et al., 2007; Jones et al., 2001, 2007); however, the understanding of its biological significance is still nascent.

Spontaneous activity in sensory neurons has been shown to serve several functions. Neurons of the lateral geniculate nucleus that synapse in the visual cortex are highly spontaneously active. Spontaneous activity keeps these synapses in a state of saturated synaptic depression (Boudreau and Ferster, 2005). As a consequence, geniculocortical synapses show no further depression in response to long and temporally complex visual stimuli. Neurons of the pretectal nuclear complex generate spontaneous firing intrinsically (Prochnow and Schmidt, 2004). Spontaneous activity in these neurons maintains normal function of oculomotor reflexes. In the somatosensory system, spontaneously active neurons of the zona incerta modulate responses of neurons in the posterior medial thalamus to sensory inputs (Trageser et al., 2006). Spontaneous activity of neurons in the somatosensory system is necessary for mediation of synaptic pruning (O'Leary et al., 1994).

Normal performance of the auditory system also depends upon spontaneous activity. Neurons from the medial nucleus of the trapezoid body enhance transmission across Calyx of Held synapses by introduction of spontaneous activity (Hermann et al., 2007). Analogous to the visual system, spontaneous activity improves the ability of the postsynaptic neurons to follow trains of high-frequency sound pulses and decreases recovery time following synaptic depression. Spontaneous activity is also critical for neuronal survival and for the refinement and maintenance of tonotopic maps before the onset of hearing (Walsh and McGee, 1987; Gummer and Mark, 1994; Jones et al., 2001, 2007). Although spontaneous activity is important for normal brain function, it is also important that a signal of interest is not swamped by spontaneous activity during signal processing.

Sound-evoked suppression of spontaneous activity has frequently been observed in neurons of the auditory system (Smith, 1977; Harris and Dallos, 1979; Relkin and Turner, 1988; Ebert and Ostwald, 1995; Galazyuk et al., 2005; Wehr and Zador, 2005; Portfors and Roberts, 2007; Nelson et al., 2009). Such suppression, lasting hundreds of milliseconds, has been observed in fibers of the auditory nerve (Smith, 1977; Harris and Dallos, 1979; Relkin and Turner, 1988), cochlear nucleus (Ebert and Ostwald, 1995; Portfors and Roberts, 2007), IC (Galazyuk et al., 2005; Nelson et al., 2009) and auditory cortex (Wehr and Zador, 2005). Despite the common occurrence of this phenomenon, it has not been studied systematically.

In vivo intracellular recordings in the IC have revealed hyperpolarizations that exceed the duration of the sound stimulus in many neurons (Nelson and Erulkar, 1963; Torterolo et al., 1995; Covey et al., 1996; Kuwada et al., 1997; Pedemonte et al., 1997; Voytenko and Galazyuk, 2007, 2008; Peterson et al., 2008). However, these potentials

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Abbreviations: CL, confidence limit; FM, frequency modulated; IC, inferior colliculus; mGluR, metabotropic glutamate receptor; PSTH, peristimulus time histogram.

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lasted less than 100 ms after the end of a stimulus, even in barbiturate anesthetized animals (Covey et al., 1996; Kuwada et al., 1997; Pedemonte et al., 1997). It is unclear whether long-lasting hyperpolarizations are responsible for prolonged suppressions of spontaneous firing.

The aim of this research was to determine which characteristics of a sound reduce spontaneous firing of auditory neurons and to verify the contributions of synaptic inhibition to stimulus suppression. We addressed this aim with both extracellular and intracellular recordings from IC neurons in awake bats, which served as a mammalian model. A majority of IC neurons showed suppression of spontaneous firing for hundreds of milliseconds following a short sound stimulus. An increase in stimulus sound level prolonged the duration of suppression. Intracellular recordings suggest that membrane hyperpolarization does not contribute to suppression beyond a few tens of milliseconds after stimulus offset. These data suggest that suppression is expressed at presynaptic terminals and/or elsewhere in presynaptic neurons.

EXPERIMENTAL PROCEDURES

Experimental preparation

All surgical and experimental procedures were approved by the Institutional Animal Care and Use Committee at the Northeastern Ohio Universities College of Medicine. Experimental subjects comprised 34 little brown bats, *Myotis lucifugus*. Each bat was anesthetized using isoflurane inhalation (1.5–2.0%, isoflurane administered by a precision vaporizer) prior to surgery. A midline incision of the skin over the cranium was made. The tissue overlying the skull was then removed and a small metal rod was glued to the skull using glass ionomer cement (3 M ESPE, Benco Dental, Wilkes-Barre, PA, USA). Following surgery, animals were allowed to recover for 2–3 days in individual holding cages.

Two days after surgery each bat was trained to stay inside a small plastic tube. This tube was used as animal holding device during recording sessions. We directed the head of the bat into the opening of the tube, and the animal crawled inside and stayed there for several hours without movement. Recordings were made from awake bats within a single walled sound attenuating chamber (Industrial Acoustics Company, Inc., Bronx, NY, USA). The metal rod on the head of the bat was secured to a small holder designed to restrain the head of the animal without causing distress, while the ears were unobstructed for free-field acoustic stimulation. A small hole (~50 μm) penetrating the dura was drilled in the skull overlying the IC, through which a recording electrode was inserted into the IC. Throughout the recording session, the animal was offered water periodically and monitored for signs of discomfort. After a recording session of 4–6 h, the exposed skull was covered with sterile bone wax, and the animal was returned to its holding cage. Experiments were conducted every 2–3 days for a maximum of 2 weeks. No sedative drugs were used during the recording sessions. If the animal showed any signs of discomfort, the recording session was terminated and the bat was returned to its cage.

Acoustic stimulation

We used linear downward frequency modulated (FM) sweeps that mimicked echolocation signals as our acoustic stimuli. Sounds were delivered to the bat via a free-field ultrasonic loudspeaker (Ultra Sound Advice, London, UK) located 30 cm in front of the bat. The FM sweeps fell from 80 to 20 kHz over 4 ms, with a 0.25 ms rise/fall time. The majority of IC neurons are tuned to the sound frequencies within this frequency range and respond well to downward FM sweeps (Galazyuk et al., 2005; Voytenko and Galazyuk, 2007; Wang et al., 2007). FM sweeps were presented once every 2 s at sound levels ranging from 0 to 80 dB SPL in 4 dB increments.

The outputs of the loudspeaker were measured with a 1/4-inch microphone (Brüel and Kjaer 4135) and found to be ±6 dB between 20 and 80 kHz, the frequency range used in the experiments. The parameters of the acoustic stimuli were controlled by D/A hardware and software from Tucker-Davis Technologies (System III) with a sampling rate of 200 kHz.

Pure tones were omitted as a stimulus in order to enable comparison between extracellular and intracellular recordings in awake animals. Pure tones can not be used for intracellular recordings because determining characteristic frequency of the recorded neuron is time-consuming whereas intracellular recordings from awake animals are typically short (3–4 min).

Recording procedure

Extracellular recordings. Extracellular single-unit recordings were made with borosilicate glass micropipettes (10–20 MΩ impedance, 2–3 μm tip) filled with 0.5 M sodium acetate. The electrode was positioned above the IC by means of a precision (1 μm) digital micromanipulator and lowered to the dorsal surface of the brain. The relative position of each electrode was monitored from the readouts of digital micrometers using a common reference point on the skull. Vertical advancement of the electrode was made by a precision piezoelectric microdrive from outside the sound attenuating chamber. Recorded action potentials were amplified (Dagan 2400A, Dagan Corporation, Minneapolis, MN, USA), monitored audiovisually on a digital oscilloscope (DL1640, YOKOGAWA, Newnan, GA, USA), digitized and then stored on a computer hard drive using EPC-10 digital interface and PULSE software from HEKA at a bandwidth of 100 kHz.

Intracellular recordings. Intracellular recordings were made using microelectrodes made from 1.0 mm diameter quartz pipettes (Sutter Instruments, Novato, CA, USA) filled with 1 M potassium acetate. Micropipettes, with impedance between 70 and 160 MΩ, were pulled on a micropipette puller (P2000, Sutter Instruments). The electrode was positioned above the IC by a digital micromanipulator (MP-285, Sutter Instruments) and lowered to the dorsal surface of the brain. Vertical advancement of the electrode was made by a precision microdrive (KOPF, model 660) in 2–3 μm steps. The electrode was placed on the surface of the IC using a surgical microscope (Leica MZ9.5, Leica Microsystems, Wetzlar, Germany).

Intracellular responses of IC neurons were amplified through a single channel amplifier (model IR183A, CYGNUS Technology Inc., Southport, NC, USA) and monitored on a digital oscilloscope (DL1640, YOKOGAWA, Newnan, GA, USA). Intracellular waveforms from the IR183A and sound stimuli from the Tucker Davis system were digitized, and then stored on a computer hard drive using EPC-10 digital interface and PULSE software from HEKA (HEKA Instruments Inc., Bellmore, NY, USA) at a bandwidth of 100 kHz. While searching for a cell, small (5–100 nA) current pulses of 100 ms duration were delivered through the microelectrode. Measuring the amplitude of these pulses allowed us to monitor impedance changes in the recording electrode. Such changes were used to determine whether the recording electrode was approaching an IC neuron. A sudden, negative DC shift and the presence of synaptic potentials indicated an intracellular impalement, which was often verified by passing positive current to evoke action potentials. A prolonged (>3 min), stable drop (>40 mV) in the DC level was an indicator of a stable impalement of an IC neuron. Intracellular recordings typically lasted 3–4 min (maximum 50 min). During intracellular recording cell membrane resting potentials fluctuated by less than 4 mV. Successful intracellu-

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