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SALICYLATE INDUCED NEURAL CHANGES IN THE PRIMARY AUDITORY CORTEX OF AWAKE CATS

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Abstract—Systemic administration of salicylate at high doses can induce reversible tinnitus and hyperacusis in humans and animals. For this reason, a number of studies have investigated the salicylate-induced changes of neural activity in the auditory cortex (AC); however, most previous studies of the AC were conducted on brain slices or anesthetized animals, which cannot completely represent the actual conditions. Few efforts have been made to examine the neural activity of awake animals, and only recorded the local field potential (LFP) of the AC. In this study, we recorded neural spike activities from chronically implanted electrodes in the primary AC (A1) of awake cats, and investigated the changes of neural responses to pure-tone and click-train stimuli after systemic injection of 200 mg/kg salicylate. We found that sound-evoked spike activities were significantly increased from 1 h after salicylate administration, and the increase of neural responses lasted longer than 3 days with a peak at 12 h. Salicylate not only increased the amplitude of transient responses at the onset and offset of pure-tone stimuli, but also induced a sustained response during the prolonged stimulus period and a late response at ~100 ms after stimulus offset. The significant enhancement of neural responses was observed over the entire tested frequency range (0.1–16 kHz) with a relative peak in the band of 3.2–9.6 kHz. The capability of exhibiting spikes synchronizing with successive clicks was also enhanced. All these effects were more apparent when the neurons were driven by high intensity sounds. Salicylate-administration also decreased the mean spontaneous rate in A1 units, and the decrease of spontaneous rate was larger in the units with a high initial spontaneous rate. Our data confirm that salicylate can modulate the neural activity at the cortical level and provide more information for understanding the mechanism of salicylate-induced tinnitus.
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Key words: salicylate, tinnitus, primary auditory cortex, synchronization, spike activity, hyperacusis.

It is well known that the application of salicylate at high doses produces reversible tinnitus, a phantom auditory sensation without any external sound stimulus, in humans (Halla and Hardin, 1988; Day et al., 1989; Halla et al., 1991; Hicks and Bacon, 1999) and animals (Jastreboff et al., 1988; Bauer et al., 1999; Guitton et al., 2003; Ruttiger et al., 2003). For this reason, significant effort has been made to investigate how the salicylate administration affects the auditory neural system, including the auditory nerve (Evans and Borerwe, 1982; Stypulkowski, 1990; Cazals et al., 1998; Muller et al., 2003; Ruel et al., 2008), the ventral and dorsal cochlear nucleus (Basta et al., 2008; Wei et al., 2010), the inferior colliculus (Jastreboff and Sasaki, 1986; Chen and Jastreboff, 1995; Ma et al., 2006; Sun et al., 2009), the medial geniculate body (Basta et al., 2008) and the auditory cortex (AC) (Ochi and Eggermont, 1996; Eggermont and Kenmochi, 1998; Wang et al., 2006; Yang et al., 2007; Su et al., 2009). The accumulated data suggest that salicylate can increase the neural activities in both the peripheral (Evans and Borerwe, 1982) and central auditory system (Ochi and Eggermont, 1996; Sun et al., 2009). Recently, Kizawa et al. proposed that salicylate may induce an alternation from the peripheral to the central tinnitus, because the salicylate-induced high expression of a transient receptor potential cation channel subfamily V-1 (TRPV1) occurred earlier in spiral ganglia and later in dorsal cochlear nucleus (Kizawa et al., 2010).

It should be noted that most previous studies were conducted on brain slices or anesthetized animals, which cannot completely represent the actual conditions. One study has shown that anesthetsia affected the salicylate-induced change of AC activity: ketamine increased salicylate-induced enhancement of the AC response, whereas isoflurate suppressed such enhancement (Sun et al., 2009). For this reason, it is necessary to examine the effect of salicylate on animals under awake conditions. Recently, some studies investigated the salicylate-induced neural changes in awake animals by recording the spontaneous and sound-evoked local field potential (LFP) in AC (Yang et al., 2007; Sun et al., 2009; Norena et al., 2010). Their major finding was that salicylate could induce a reversible increase in the amplitude of LFP evoked by tone bursts over a wide range of frequencies and intensities, which may be associated with salicylate-induced hyperacusis (Myers et al., 1965); however, no such effect has been demonstrated at the level of neural spike activity. To date, only one report has presented preliminary neural spike

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Abbreviations: AC, auditory cortex; CF, characteristic frequency; ICI, inter-click interval; PSTH, peri-stimulus time histogram; SPL, sound pressure level.

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data recorded from 9 U (Yang et al., 2007), showing that salicylate administration caused a reversible decrease of the spontaneous spike rate in the AC of awake rats. In order to systemically investigate how the AC activities of awake animals are affected by salicylate administration, we conducted extracellular recording in the primary auditory cortex (A1) of awake cats using chronically implanted electrodes, and examined the changes of neural responses to pure-tone and click-train stimuli after systemic injection of 200 mg/kg salicylate. Our results provided more accurate information about the effect of salicylate.

EXPERIMENTAL PROCEDURES

Animal preparation

All procedures were approved by the University of Yamanashi Animal Care and Use Committee. Animal preparation and recording procedures were similar to those used in our previous experiments (Qin et al., 2007, 2008a,b, 2009). The cats were premedicated with 0.1–0.2 ml atropine sulfate (0.5 mg/ml) s.c. After about 30 min they received an i.m. injection of 25 mg/kg ketamine hydrochloride (50–100 mg/ml) and an i.p. injection of 20 mg/kg sodium pentobarbital (50 mg/ml). The cat was then fixed to a stereotaxic frame (SN-3N; Narishige). The head was shaved and an incision was made in the skin overlying the skull. The skin flap was removed and the skull cleared from overlying muscle tissue. The position of A1 was marked on the bone surface according to stereotaxic coordinates. Four small holes were drilled over the occipital bone and fine jeweler's screws were inserted to serve as an anchor for a metal block that was cemented to the skull with dental acrylic. After the cement had hardened, the head was held through the metal block and the ear bars were removed. We then drilled several small holes (0.5–1 mm diameter) in the temporal bone above the potential location of A1. A tungsten microelectrode (diameter: 250 μm; impedance: 2–5 MΩ at 1 kHz; FHC Inc.) was advanced into the cortex using a micromanipulator to examine the neural responses to tonal stimuli at each site. According to the characteristics of tonotopic gradient, we identified the location of A1.

Electrode implant

We implanted a microwire array following the method developed by Jackson and Fetz (Jackson and Fetz, 2007). The microware consisted of 12 (2×6) Teflon-insulated 50 μm diameter tungsten wires (part #795500; A-M Systems, Carlsborg, WA, USA) running inside polyamide guide tubes of 225 μm internal diameter (part #822200; A-M Systems). The tip impedance of each wire was around 0.5 MΩ at 1 kHz. For implantation, a 5×3 mm craniotomy was made at the location of A1 with a dental bur. The microwire array was then lowered into position on a stereotaxic carrier so that the ends of the guide tubes rested just above the dura mater over the low frequency (<16 kHz) area of A1. Wires were individually inserted into the cortex, while viewing through a microscope and listening to an audio monitor of the recorded signal. Once all microwires had been inserted, the craniotomy was tightly filled with gelfoam and sealed using dental cement. Plastic casing was attached with further skull screws and cement.

Acoustic stimulus presentation

The sound waveform was digitally generated by user-written programs in a MATLAB (Mathworks) environment. The signals were fed into a 16-bit digital-to-analog converter (PCI-6052E; National Instruments) at a sampling frequency of 100 kHz. Bilateral acoustic stimuli were played through a pair of speakers (K1000; AKG) placed 2 cm from the auricles of cats. The sound pressure level (SPL; in decibels re. 20 μPa) was measured using a Bruel and Kjaer 1/2" condenser microphone with a preamplifier 2669 situated at the position of the cat's ear. We calibrated the sound delivery system between 0.1 and 16 kHz in frequency steps of 8 Hz, and the output varied by $\pm$5 dB. Harmonic distortion was less than $-$60 dB.

We used two stimulus ensembles to evaluate sound-driven neural activity. One was the pure-tone ensemble which randomly presented 125 single tones (160 ms in duration, including 5 ms rise/fall time) in the frequency range of 128–16,000 Hz (in 128 Hz steps) and at 20, 40 and 60 dB SPLs, respectively. The other consisted of 320 ms duration click-trains. The individual clicks were 0.1 ms rectangular electric pulses. The inter-click interval (ICI) was randomly selected among 80, 60, 40, 20, 10 and 5 ms. Each ICI was repeated 12 times, constructing an ensemble of 72 stimuli. The maximum click level was calibrated to that of the pure-tone wave at 60 or 20 dB SPL. The inter-stimulus intervals were randomly set between 1 and 3 s.

Electrophysiological recording

After 2–3 weeks of postoperative recovery and adaptation training, the recording experiment was conducted in an electrically shielded, sound-attenuated chamber. During the recording period, the cats were immobilized on a custom-built frame, and passively listened to auditory stimuli. A video camera was placed in front of the cat to monitor its state. If a sign of drowsiness (eye closing or drifting) was detected, the cat was alerted by gently tapping the body using a remote-controlled tapping tool, or by briefly opening and closing the door.

Multi-channel neural recording was performed using hardware and software from Tucker-Davis Technologies (TDT, Alachua, FL, USA). The microwire output was connected to a multichannel preamplifier (RA16PA; TDT) using a flexible, low noise cable. The output of the preamplifier was delivered to a digital signal processing module (RX-7; TDT). Spike activities were discriminated using principal component feature space spike-sorting software (SpikePac; TDT). Using this method, 1–3 single units could be well isolated from each channel. The time stamps of these single units were stored and coded separately. As described by Jackson and Fetz (Fitzgerald et al., 2007), clean single units could often be followed for up to several weeks after positioning the microwires; however, in some cases, cells were lost during recording and new cells also occurred. Because we were not confident that all the data sets tracked the same units during the observing period, in this study we pooled the separable single-unit spike trains of each channel, again constructing multiunit data. As shown in the example (Fig. 1A), the response properties of the multiunit activities were similar between pre-administration and after recovery from salicylate administration, suggesting that our recording was stable throughout this period.

Data analysis

Spike activities driven by pure-tone stimuli were aligned along the stimulus onset, constructing a raster plot of each tone frequency (Fig. 1A). The peri-stimulus time histogram (PSTH), counting the spikes across the 125 trials of different frequencies, was computed in 1 ms bin width and smoothed by Gaussian function with 5 ms SD (Fig. 1B). The neural responses of pure-tone stimuli were analyzed in four segments: "onset" response (during 0–50 ms after stimulus onset), "sustained" response (from 50 ms after stimulus onset to stimulus offset), "offset" response (0–50 ms after stimulus offset) and "late" response (50–150 ms after stimulus offset). The tuning curves of each kind of responses were constructed by plotting the average firing rate in the "onset", "sustained", "offset" or "late" segment, respectively, against tone frequency in a linear step of 128 Hz (Fig. 2A–D). The threshold to identify a significant

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