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Research paper

Forward acoustic masking enhances the auditory brainstem response in a diotic, but not dichotic, paradigm in salicylate-induced tinnitus

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ABSTRACT

We recently reported that forward acoustic masking can enhance the auditory brainstem response (ABR) in rats treated with a high dose of sodium salicylate (NaSal), a tinnitus inducer, when tested in open acoustic field (Liu and Chen, 2012, Brain Research 1485, 88–94). In the present study, we first replicated this experiment in closed acoustic field under two conditions: (1) the forward masker and the probe were presented to both ears (diotic paradigm); (2) the forward masker was presented to one ear and the probe to the other ear (dichotic paradigm). We found that only when the stimuli were presented by using the diotic, rather than the dichotic, paradigm could forward acoustic masking enhance the ABR in the rat treated with NaSal (300 mg/kg). The enhancement was obvious for ABR waves II and IV, but not for wave I, indicating a central origin. The enhancement occurred at the high frequencies (16, 24, 32 kHz) at which the animals demonstrated a tinnitus-like behavior as revealed by using the gap prepulse inhibition of acoustic startle paradigm. We then administered vigabatrin, a GABA transaminase inhibitor, in the animals to suppress NaSal-induced tinnitus. The vigabatrin treatment successfully prevented forward acoustic masking from enhancing the ABR. These findings demonstrate that the observed enhancement of ABRs by forward acoustic masking originates in the central auditory pathway ipsilateral to the stimulated ear. We propose that the enhancement is closely associated with NaSal-induced tinnitus.

1. Introduction

Tinnitus is a phantom auditory sensation in the absence of an external sound (Henry et al., 2005; Hoffmann and Reed, 2004). Although tinnitus is a very prevalent auditory disorder that affects the quality of life of millions of people (Axelsson and Ringdahl, 1989; Shargorodsky et al., 2010; Tyler and Baker, 1983), there is no satisfactory treatment in most cases and no single FDA-approved drug available yet (Langguth and Elgoyhen, 2012). To change this situation, medical doctors and research scientists need reliable and efficient measures of tinnitus for evaluation of treatment outcomes, for studying underlying mechanisms and for screening of drugs. Currently, tinnitus loudness, frequency and severity are often assessed based on the subjective report of the patient in the clinic (Vernon and Meikle, 2003; Ward et al., 2009). The nature of tinnitus in animal models is assessed largely through observation of behavioral responses in the laboratory (Jastreboff and Sasaki, 1994, Jastreboff et al., 1988; Turner, 2007; Turner et al., 2006). Most of these models involve tedious and time-consuming behavioral training and severely depend on the animal's cognitive and motor functions. Thus, there is a need to develop an alternative objective approach to measuring the subjective tinnitus.

Evoked or spontaneous auditory neural activities in tinnitus have been extensively studied to determine the neural correlates or index of tinnitus (Chen and Jastreboff, 1995; Eggermont, 2005; Eggermont et al., 1998; Melcher et al., 2009; Norena et al., 2003; Yang et al., 2007). However, most of the reported neural signatures for tinnitus are not specific and cannot practically be used as objective indicator of tinnitus. We recently found and reported that

Abbreviations: ABR, auditory brainstem response; FMI, forward masking index; GPIAS, gap prepulse inhibition of acoustic startle; NaSal, sodium salicylate; RMS, root mean square; VGB, vigabatrin

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forward acoustic masking can enhance, rather than suppress, the auditory brainstem response (ABR) to a probe tone in an animal model with tinnitus induced by a high dose of sodium salicylate (NaSal) when tested in open acoustic field (Liu and Chen, 2012). The enhanced ABR by forward acoustic masking suggests a promising objective measure of subjective tinnitus. In the present study, we replicated this experiment in closed acoustic field under two conditions: (1) the forward masker and the probe were presented to both ears (diotic paradigm); (2) the forward masker was presented to one ear and the probe to the other ear (dichotic paradigm). We found that only when the stimuli were presented by using the diotic, rather than the dichotic, paradigm could forward acoustic masking enhance the ABR in NaSal-induced tinnitus. We further found that administration of vigabatrin, a GABA transaminase inhibitor, could eliminate the ABR enhancement in NaSal-induced tinnitus.

2. Methods

2.1. Subjects

Data were collected from 69 Wistar rats of either sex aging from 2 to 5 months and weighing from 300 to 550 g. The rats were purchased from Vital River Laboratories, Beijing, China. Of these animal subjects, 33 were treated with NaSal and had ABRs measured from them in the diotic condition (Figs. 2–5; Supplementary Fig. 2) and 10 in the dichotic condition (Figs. 6 and 7). Six rats were treated with NaSal and had the gap prepulse inhibition of acoustic startle (GPIAS) measured from them (Fig. 8). Nine rats were treated with vigabatrin plus NaSal and had ABRs measured from in the diotic condition (Fig. 9; Supplementary Fig. 3). Eleven rats had ABRs measured for estimation of hearing threshold shifts after NaSal treatment (Supplementary Fig. 1). The protocols used in this study followed and were approved by the Institutional Animal Care and Use Committee of University of Science and Technology of China. All the efforts were made to minimize the number of animals used and the suffering of animals.

2.2. Acoustic stimuli

All acoustic stimuli used in this research were programmed with RpvdsEx v7 (Tucker–Davis Technologies, USA) and MatLab R2008a (MathWorks Inc, USA), and generated with TDT System 3 hardware (RP 2.1, PA 5, ED 1, HB 7). The acoustic signals were converted into electrical signals by a microphone (Model 7016, ACO Pacific, Inc. USA) and acquired by the TDT System for calibration of sound levels. A forward acoustic masker and a probe tone burst were produced for measuring the acoustic masking effects on the ABR. The forward masker was a bandpass noise (2.5 ms rise/fall time, $\cos^2$ ramp, 1 kHz bandwidth) at 50 dB SPL. The center frequency of the forward masker was 6 kHz, 12 kHz, 16 kHz, 24 kHz or 32 kHz. The probe was a tone burst (2 ms rise/fall time, $\cos^2$ ramp) at 70 dB SPL with a duration of 5 ms. The frequency of the probe was the same as the center frequency of the acoustic masker. The intervals between the forward masker and the probe tone were varied as follows: infinity (no forward masker), 80 ms, 50 ms, 20 ms, 10 ms and 0 ms. The masker and the probe were presented at a rate of 400 times per minute.

The forward masker and the probe tone were presented with a TDT electrostatic speaker EC 1 which delivers the acoustic stimuli into the animal's ear canal through a tube in a close field either diotically or dichotically (Fig. 1A). In the diotic condition, the probe and the masker were presented to both ears (diotic paradigm). In the dichotic condition, the probe was presented only to right ear and the masker only to left ear (dichotic paradigm).

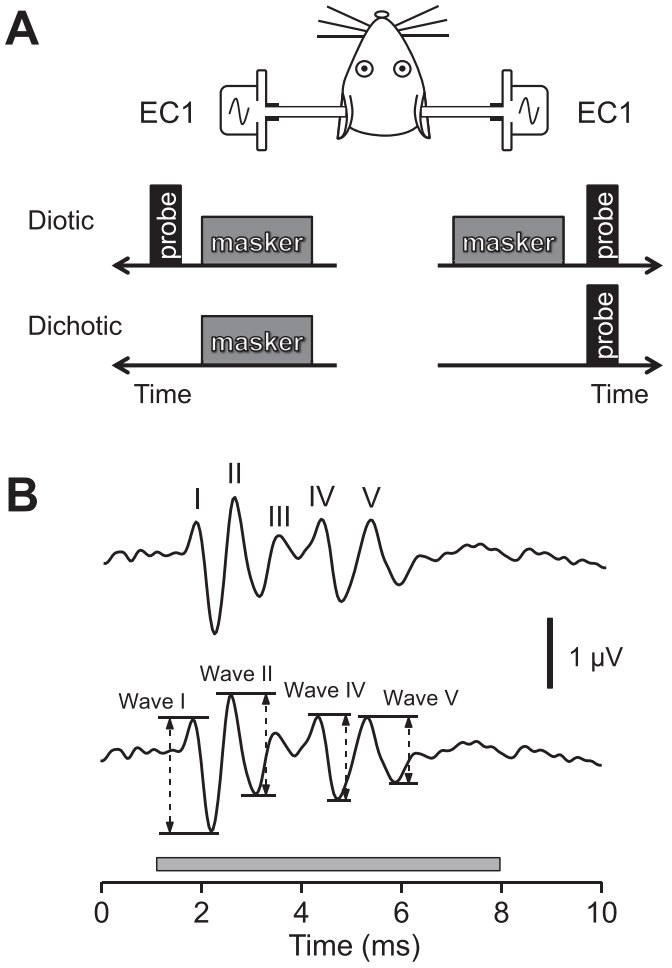

Fig. 1. (A) Schematic diagram illustrating the diotic stimulation paradigm and dichotic stimulation paradigm. The acoustic stimuli were delivered to the ears of rats using two electrostatic speakers (TDT EC 1) in a closed field. In the diotic paradigm, the probe and the masker were presented to both ears. In the dichotic paradigm, the probe only presented to the right ear and the masker only to the left ear. (B) A sample ABR to a 24 kHz, 70 dB SPL tone burst with waves I, II, III, IV and V identified (upper panel). Peak-to-peak amplitude was calculated for waves I, II, IV and V. RMS amplitude was calculated within a time window 1–8 ms (horizontal bar) from the stimulus onset (lower panel). ABR, auditory brainstem response; RMS, root mean square.

2.3. ABR recording

For recording the ABR, the rats were sedated with chloral hydrate (400 mg/kg, i.p.) and placed on a soft pad in a soundproof chamber. Four subcutaneous stainless-steel needle electrodes were positioned at the vertex (negative), left mastoid (positive channel 1), right mastoid (positive channel 2) and nose tip (ground) of the animal. The resistance between each electrode and the ground electrode was less than 1 kΩ. The ABRs to the probe tone were recorded with TDT RA16 and stored on a computer for real-time and off-line analysis. The sampling frequency was 25 kHz and the signal was notch-filtered at 50 Hz, high pass filtered at 0.3 kHz and low pass filtered at 3 kHz. The original data of 200 sweeps were averaged to increase signal to noise ratio. Each ABR wave was visually identified.

Both root mean square (RMS) and peak-to-peak magnitude were calculated as the ABR amplitude. The RMS was calculated within a time window 1–8 ms from the onset of the probe stimulus. The peak-to-peak amplitudes were calculated for waves I, II, IV and V (Fig. 1B). Hearing threshold was estimated by visually identifying the distinct ABR that could be evoked with the lowest sound