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Research Report

Altered brainstem auditory evoked potentials in a rat central sensitization model are similar to those in migraine

Xianghong Arakaki[a,*], *Gary Galbraith*[b], *Victor Pikov*[c], *Alfred N. Fonteh*[a], *Michael G. Harrington*[a,*]

[a]*Molecular Neurology Program, Huntington Medical Research Institutes, 99 North El Molino Avenue, Pasadena, CA 91101, USA*

[b]*Mental Retardation Research Center, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California at Los Angeles, USA*

[c]*Neural Engineering Program, Huntington Medical Research Institutes, 734 Fair mount Avenue, Pasadena, CA 91101, USA*

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ABSTRACT

Migraine symptoms often include auditory discomfort. Nitroglycerin (NTG)-triggered central sensitization (CS) provides a rodent model of migraine, but auditory brainstem pathways have not yet been studied in this example. Our objective was to examine brainstem auditory evoked potentials (BAEPs) in rat CS as a measure of possible auditory abnormalities. We used four subdermal electrodes to record horizontal (h) and vertical (v) dipole channel BAEPs before and after injection of NTG or saline. We measured the peak latencies (PLs), interpeak latencies (IPLs), and amplitudes for detectable waveforms evoked by 8, 16, or 32 kHz auditory stimulation. At 8 kHz stimulation, vertical channel positive PLs of waves 4, 5, and 6 (vP4, vP5, and vP6), and related IPLs from earlier negative or positive peaks (vN1–vP4, vN1–vP5, vN1–vP6; vP3–vP4, vP3–vP6) increased significantly 2 h after NTG injection compared to the saline group. However, BAEP peak amplitudes at all frequencies, PLs and IPLs from the horizontal channel at all frequencies, and the vertical channel stimulated at 16 and 32 kHz showed no significant/consistent change. For the first time in the rat CS model, we show that BAEP PLs and IPLs ranging from putative bilateral medial superior olivary nuclei (P4) to the more rostral structures such as the medial geniculate body (P6) were prolonged 2 h after NTG administration. These BAEP alterations could reflect changes in neurotransmitters and/or hypoperfusion in the midbrain. The similarity of our results with previous human studies further validates the rodent CS model for future migraine research.

*Corresponding authors. Fax: +1 626 795 5774.
E-mail addresses: xianghong@hmri.org (X. Arakaki), mghworks@hmri.org (M.G. Harrington).

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1. Introduction

Migraine affects more than 30 million people in the United States who suffer from episodes lasting hours to days (Mueller, 2007). The symptoms include: severe headache, nausea, cognitive impairment, and discomfort from normal light, sound, and smells (Buse et al., 2012; Charles and Brennan, 2010; Goadsby et al., 2009; Noseda and Burstein, 2013; Woodhouse and Drummond, 1993). The migraine pathophysiology is not fully elucidated, though several brain circuits have been implicated (Goadsby et al., 2009; Noseda and Burstein, 2013). Auditory symptoms are prominent in migraine and are the focus of this study; they include fluctuating low-frequency hearing loss, sudden deafness, auditory hallucinations, tinnitus, and phonophobia. Significant phonophobia is often found in interictal migraine and worsened during ictal migraine compared to controls (Ashkenazi et al., 2009; Vingen et al., 1998).

Approaches to investigate auditory function include basic audiological evaluation such as initial otoscopic examination, standard pure tone audiometry, speech audiometry, tympanometry, distortion product otoacoustic emission, and others (Hamed et al., 2012). It is hard to measure the auditory function behaviorally in the rat, but it can be readily measured by evoked potentials (EPs) *in vivo*. Auditory EPs include the following three categories based on their response latencies (Quian, 2006), all of which have been found changed in migraine.

Early EPs include the electrocochleogram and brainstem auditory evoked potentials (BAEPs). The electrocochleogram has latencies of less than 2.5 ms and reflects responses from the auditory nerve and cochlea. BAEPs reflect responses from the brainstem with latencies less than 12 ms (Quian, 2006). Studies by Dash et al. (2008) suggest that BAEP abnormality may be the earliest auditory indication in migraine since all migraineurs with auditory symptoms have prolonged peak latencies (PLs) and/or interpeak latencies (IPLs) in BAEP recordings. Studies in children with headache, however, did not find significant BAEP changes between migraineurs and controls (Unay et al., 2008).

Middle latency EPs have latencies between 12 and 50 ms. Middle latency auditory evoked potentials lacked auditory sensory gating in migraine patients, results that were considered to stem from a hypofunction of monoaminergic subcortico-cortical connections (Ambrosini et al., 2001).

Late, or cortical, EPs have latencies between 50 and 250 ms. Auditory evoked cortical potentials show potentiation or lack of habituation in interictal migraineurs instead of the habituation found in healthy controls, and the intensity dependence of auditory evoked cortical potentials is higher in migraineurs (Afra et al., 2000; Ambrosini et al., 2003). The lack of habituation of auditory evoked potentials is thought to be due to a decreased pre-activation level of the sensory cortex (Afra et al., 2000; Coppola et al., 2009; Wang and Schoenen, 1998).

Nitroglycerin (NTG)-induced central sensitization (CS) in rodents (Harrington et al., 2011; Tassorelli et al., 1996; Tassorelli et al., 2005) is a widely accepted migraine model. Besides triggering migraine in humans (Olesen, 2010), NTG causes hyperalgesia and allodynia (Harrington et al., 2011; Oshinsky and Luo, 2006), photophobia and meningeal dilatation in mice (Markovics et al., 2012); cFos expression in the trigeminal pathway and brain sodium elevation after NTG injection (Harrington et al., 2011) in rats. Many of the symptoms were reversed by sumatriptan (Bates et al., 2010; Ramachandran et al., 2012; Read et al., 1999). The overall aim of our study is to determine whether BAEPs in this CS model have similar changes to those in migraine, and whether they add objective and functional information to help in understanding the early sensory changes in this migraine model. For this purpose, we measured the BAEP peaks, PLs, IPLs, and amplitudes in rats that were given an intraperitoneal (ip) injection of either saline or NTG.

The rodent auditory system is more dominant than the visual system, and is easier to test (Martin et al., 2006; Yang et al., 2008; Yang and Zador, 2012). Rodent BAEPs, similar to those in humans, have a series of waves that reflect the synchronous short-latency synaptic activity along the brainstem auditory pathway. These 5–6 positive peaks are thought to represent the activity in the following auditory processing centers: auditory nerve (P1), posterior anteroventral cochlear nucleus (AVCN) (P2), anterior AVCN and cells of the contralateral medial nucleus of the trapezoid body (P3), bilateral medial superior olivary nuclei (P4), lateral lemniscus and/or inferior colliculus (P5), and the more rostral structures such as the medial geniculate body (P6) (Henry, 1979; Parham et al., 2001; Shaw, 1988).

2. Results

Examples of horizontal and vertical channel BAEPs at 8, 16, and 32 kHz stimulation frequencies are shown in Fig. 1. The BAEP measurements were similar in shape and amplitude to those recorded by other laboratories (Galbraith et al., 2006; Jirka et al., 1985; Liu et al., 2011; Rice et al., 2011). As shown in Fig. 1, BAEP horizontal channel P1 and P2 from all frequencies were clear. However, BAEP vertical channel peaks P5 and P6 at 16 kHz stimulation and vertical peaks P3–P6 at 32 kHz stimulation were missing. Thus only a subset of BAEP peaks was discernible and analyzed. At 8 kHz stimulation, horizontal channel P1 and P2 and vertical channel N1, P2–6 were studied (Fig. 1A). At 16 kHz stimulation, horizontal channel P1 and P2 and vertical channel N1, P2–4 were measured (Fig. 1B). At 32 kHz stimulation, horizontal channel P1 and P2 and vertical channel N1 and P2 were studied (Fig. 1C).

The PLs and IPLs from NTG and saline groups at different frequency stimulations were compared in detail in the following paragraphs. Briefly, later PLs and related IPLs significantly increased in the NTG group compared with the saline group, but only at 8 kHz in the vertical channel. The NTG or saline treatment/time interaction was significant ($p=0.001$); therefore, the drug effect was tested at each time individually.

In saline-treated rats at 8 kHz stimulation, horizontal channel hP1–hP2 latencies and vertical channel vN1 and vP2–vP6 latencies were slightly increased with time, but were not significantly different from the baseline (Figs. 2A and 3; Table 1). The hPL2 in the NTG group was decreased 1 h after injection as well as before the NTG injection ($p<0.05$)