Hearing Research 310 (2014) 69–75

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research paper

Auditory responses to electric and infrared neural stimulation of the rat cochlear nucleus

Rohit U. Verma [a,c,f], Amélie A. Guex [d], Kenneth E. Hancock [c], Nedim Durakovic [c], Colette M. McKay [b,e], Michaël C.C. Slama [c,f], M. Christian Brown [c,f,*], Daniel J. Lee [c,f]

[a] School of Medicine, University of Manchester, UK
[b] School of Psychological Sciences, University of Manchester, UK
[c] Eaton-Peabody Laboratories, Massachusetts Eye and Ear Infirmary, USA
[d] Ecole Polytechnique Fédérale de Lausanne, Switzerland
[e] The Bionics Institute of Australia, Melbourne, Australia
[f] Department of Otology and Laryngology, Harvard Medical School, Boston, MA 02114, USA

ARTICLE INFO

Article history:
Received 15 November 2013
Received in revised form
11 January 2014
Accepted 20 January 2014
Available online 5 February 2014

ABSTRACT

In an effort to improve the auditory brainstem implant, a prosthesis in which user outcomes are modest, we applied electric and infrared neural stimulation (INS) to the cochlear nucleus in a rat animal model. Electric stimulation evoked regions of neural activation in the inferior colliculus and short-latency, multipeaked auditory brainstem responses (ABRs). Pulsed INS, delivered to the surface of the cochlear nucleus via an optical fiber, evoked broad neural activation in the inferior colliculus. Strongest responses were recorded when the fiber was placed at lateral positions on the cochlear nucleus, close to the temporal bone. INS-evoked ABRs were multipeaked but longer in latency than those for electric stimulation; they resembled the responses to acoustic stimulation. After deafening, responses to electric stimulation persisted, whereas those to INS disappeared, consistent with a reported "optophonic" effect, a laser-induced acoustic artifact. Thus, for deaf individuals who use the auditory brainstem implant, INS alone did not appear promising as a new approach.

1. Introduction

The auditory brainstem implant (ABI) is the primary rehabilitative option for deaf patients who cannot receive the cochlear implant due to damage of the auditory nerve (from a tumor, surgery or trauma), scarring of the cochleae, or severe inner ear dysplasia. In the ABI, a surface electrode array bypasses the auditory nerve and electrically stimulates the cochlear nucleus (CN). Unlike most cochlear implant users, the majority of ABI users do not achieve open set word recognition (Colletti et al., 2012; Otto et al., 1998). A number of theories have been proposed to explain these differences, including damage to the CN from tumor growth or surgery to remove a tumor, limited access to the tonotopic organization of the CN with surface stimulation, suboptimal placement of the electrode array, and poor spatial specificity associated with electric current spread (Colletti and Shannon, 2005; Otto et al., 1998; Shannon et al., 1993). Consistent with the latter two ideas, ABI users often experience side effects from stimulation of non-auditory pathways, resulting in facial nerve symptoms, dizziness, throat and tongue sensations and limb pain (Shannon et al., 1993). Electrodes with such side effects must be turned off when the ABI processor is programmed.

Infrared neural stimulation (INS) is a technique in which pulsed infrared radiation produced by a laser is used to stimulate neural tissue. This technique has been applied to the sciatic nerve (Wells et al., 2007b), cavernous nerves (Fried et al., 2008), facial nerve (Teudt et al., 2007), vestibular nerve (Harris et al., 2009), and the cochlea (Izzo et al., 2006, 2007; Richter et al., 2008). The INS method may be more spatially selective than electric stimulation. For example, INS applied to different portions of the sciatic nerve evokes contraction in different muscle groups (Wells et al., 2007a),

Abbreviations: ABI, auditory brainstem implant; ABR, auditory brainstem response; AN, auditory nerve; AVCN, anteroventral subdivision of the cochlear nucleus; CN, cochlear nucleus; CF, characteristic frequency; DCN, dorsal subdivision of the cochlear nucleus; eABR, electrically evoked auditory brainstem response; IC, inferior colliculus; INS, infrared neural stimulation; PVCN, posteroventral subdivision of the cochlear nucleus; SPL, sound pressure level; VN, vestibular nerve

* Corresponding author. Eaton-Peabody Laboratory, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114, USA. Tel.: +1 617 573 3875; fax: +1 617 720 4408.
E-mail address: Chris_Brown@meei.harvard.edu (M.C. Brown).

0378-5955/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.heares.2014.01.008

presumably because it only stimulates the part of the nerve within the optical beam path. In the auditory system, INS applied to the cochlea evokes midbrain responses with spatial tuning curves that can be as narrow as those evoked by acoustic tones (Richter et al., 2011). However, INS has not been previously applied to the CN, and whether it evokes responses in a broad or narrow pattern is not known.

In this study, using a rat model, we applied INS to the CN. The response metrics used were the auditory brainstem response (ABR) and neural responses in the inferior colliculus (IC). The ABR neural generators, at least to acoustic stimuli, are specific populations of auditory neurons in the ventral subdivision of the CN, the superior olivary complex, and inferior colliculus that respond with temporal synchrony (Melcher and Kiang, 1996). The neural responses from the IC, by contrast, may be less dependent on synchrony and likely reflect the inputs from both the dorsal and ventral CN subdivisions (Oliver, 1984; Schofield, 2001) as well as inputs from the superior olivary complex (Glendenning et al., 1992; Schofield, 2002). To compare to INS responses, we also evoked responses to electric stimulation, which is the method of exciting neurons used by the ABI. An electrically evoked response (eABR) consists of several waveform peaks (Abbas and Brown, 1988, 1991; Nevison, 2006; O'Driscoll et al., 2011; van den Honert and Stypulkowski, 1986; Waring, 1995; Waring et al., 1999), but has shorter latency than its acoustically evoked counterpart. Electric stimulation of the CN also evokes strong neural responses in the IC (Hoa et al., 2008; McCreery et al., 1998; Shivdasani et al., 2008). By using both hearing and deafened preparations, we studied which portions of these responses were due to the "optophonic" phenomenon associated with the use of a pulsed infrared radiant laser source (Teudt et al., 2011). Our overall conclusions are that, used alone, INS does not seem to offer a clear avenue toward improving the ABI.

2. Materials and methods

2.1. Anesthesia and surgery

All procedures were conducted in accordance with guidelines of the NIH and were approved by the Animal Care and Use Committee of the Massachusetts Eye and Ear Infirmary and Harvard Medical School. Experiments were conducted within a sound-attenuating chamber. Data were obtained from 30 adult male Sprague–Dawley rats (370–600 g). Anesthesia was ketamine (100 mg/kg i.p.) and xylazine (20 mg/kg i.p.). Atropine (0.4 mg/kg) was given to minimize respiratory secretions. Dexamethasone (0.8 mg/kg) was administered at induction to minimize brain swelling during surgery. Booster injections of ketamine (30 mg/kg i.p.) and/or xylazine (6 mg/kg i.p.) were given every hour as required after paw pinch assessment.

A tracheal cannula was placed, and the rat was positioned on a warming pad and placed on an animal platform in a stereotactic head holder with bars that stabilized the head placed rostral to the ear canals (David Kopf Instruments, Tujunga, CA). A posterior craniectomy was created and the dura overlying the left cerebellum was exposed. The dura was incised with a cruciate incision and surface blood vessels on the cerebellum thermo-cauterized. The left half of the cerebellum was gently aspirated to successively reveal the left CN and associated brainstem at the caudal end of the fourth ventricle. The exposed brainstem surface was kept moist by the application of 0.9% NaCl and covered with gelfoam. A separate mini-craniotomy was performed over the right temporo-parietal suture, rostral to the tentorium. After incision of the dura, this craniotomy provided access to the IC. A closed-field sound system was placed in the left ear canal. In 6 animals, after pre-deafening data were collected, a cut was made of the left auditory nerve at the central edge of the internal auditory meatus to deafen the animal on that side.

2.2. Electric and infrared neural stimulation

Electric current pulses were delivered to the surface of the left CN using a pair of stainless steel wires insulated except at the tip (200 μm diam.; impedance 0.1–0.5 MΩ). Bipolar, biphasic pulses (100 μs duration) were presented through a stimulus isolator (Model 2200, A-M Systems, Carlsborg, WA) at 27 pulses/s. Infrared pulses for INS were generated using a diode laser (Capella R-1850, Lockheed-Martin Aculight Corp., Bothell, WA). The laser unit was kept outside the sound-attenuating chamber and the optical fiber (400 μm diam.) was led into the chamber via a penetration hole. The distal fiber was mounted to a three-axis micromanipulator and its tip was placed on the surface of the left CN. Unless explicitly stated otherwise, laser parameters were: pulse duration of 0.25 ms, stimulation rate of 23 Hz, and wavelength of 1849 nm. This wavelength is expected to penetrate into the tissue about 700 μm (Hale and Querry, 1973). Radiant energy of the laser was measured with a high-sensitivity thermopile sensor (PS19Q, Coherent, Santa Clara, CA).

2.3. IC Recordings

Multi-unit recordings were made with a 16 channel penetrating electrode array (A1x16-5 mm-150-177, Neuronexus, Ann Arbor, MI), with a global reference. The array was inserted into the central part of the right IC through the overlying occipital cortex using a 3-D micromanipulator (David Kopf Instruments Tujunga, CA) bolted to the head holder. Electrode insertion was in a dorsal to ventral trajectory along the tonotopic axis of the IC. Correct placement was confirmed by neural responses recorded across the full length of the array during acoustic stimulation to the left ear using tone pips (20 ms duration; 1–32 kHz in increments of 2 steps per octave).

For the IC recordings, after sampling with 16-bit resolution at 20 kHz, analysis of the raw data was performed with programs written with Matlab software (The Mathworks Inc., Natick, MA). Signal was high-pass filtered with a forward and reverse Butterworth filter of order 5 with a 500 Hz cut-off frequency, and spikes were detected when the signal exceeded a threshold defined as four times the median of the signal containing spontaneous activity. Spontaneous activity was measured in each recording as the spike count with no stimulation. The time window for counting spikes was the interval from 5 to 25 ms after stimulus onset. The number of spikes was averaged over 32 trials. Activation was defined as the mean spike count across all electrodes for each stimulation level.

2.4. ABR Recordings

ABRs were recorded between needle electrodes placed subcutaneously at the vertex and the left (ipsilateral) ear, with a ground electrode placed on the back. The signal was filtered with an analog bandpass filter (30 Hz–3 kHz), amplified by 60 dB (Ithaco Model 1201, DL Instruments, Ithaca NY), A/D converted (sampling at 25 kHz) and averaged (acoustic: 512 avgs; electric: 100 avgs; INS: 512 avgs). The first millisecond of electrically generated ABR signals, containing the stimulus artifact, was ignored. The INS-generated ABRs were digitally filtered with a forward and reverse band-pass Butterworth filter of order 5, with cut-off frequencies of 200 and 2.5 kHz. The RMS of the first 10 ms of the ABR waveform was calculated with Matlab software.