Evoked Potentials in Response to Electrical Stimulation of the Cochlear Nucleus by Means of a Multi-channel Surface Microelectrode

Kiyoshi Oda, Tetsuaki Kawase*, Daisuke Yamauchi, Yukio Katori, and Toshimitsu Kobayashi

* Associate Professor
Department of Otolaryngology-Head and Neck Surgery, Graduate School of Medicine
E-mail: kawase@orl.med.tohoku.ac.jp

Abstract

The auditory potentials in response to electrical stimulation of the cochlear nucleus using a multi-channel surface microelectrode (MED 64 system), in which the inter-electrode distance is 100 μ m, were examined in guinea pigs. Even when surface bipolar stimulations with this very short separation of two electrodes are employed, the unequivocal waves of electrically evoked auditory brainstem responses (EABRs), which increased in amplitude with increasing stimulation current, were constantly derived.

Preliminary results of electrophysiological mapping using the MED 64 system indicated that more precise electro-physiological mapping may be possible based on the EABR threshold distribution using bipolar stimulation with the very short separation.

1. Introduction

Auditory brainstem implants (ABI) are an artificial organ technology in which electrodes are implanted in the brainstem in order to restore the hearing of patients who have lost their hearing as a result of auditory nerve dysfunction [1]. Cochlear implants, which bypass the inner ear and provide information to the hearing centers through direct stimulation of the auditory nerve [2], have already come into wide clinical use in Japan. In contrast, ABI attempt to restore auditory function by directly stimulating the cochlear nucleus in the auditory brainstem.

Auditory brainstem implants are primarily indicated in the case of neurofibromatosis type II, a hereditary autosomal dominant disorder which typically presents as bilateral acoustic neurofibromatosis. This disorder is recognized by the Japanese Ministry of Health, Labor and Welfare as a specified disease whose treatment qualifies for special government subsidies (incidence: 1/35,000). Patients with this disorder typically lose their hearing sooner or later as the tumor increases in size, and until now no effective treatment has been available for patients once they have lost their auditory function. As a result, patients suffering from this disorder are subject to a great deal of misery and anxiety.

In recent years the clinical application of cochlear implants has been very effective in restoring the hearing of patients with cochlear hearing loss, but they are not effective in the case of diseases such as the one described

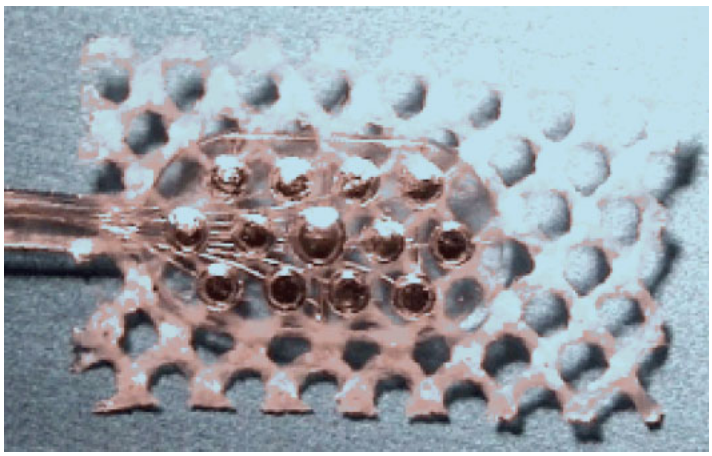


Fig. 1. Electrode of an auditory brainstem implant (MED-EL^{R} Surface electrode)
Dimensions: 5.5 mm x 3 mm x 0.6mm (thickness); number of electrodes: 12. The device is placed on the surface of the auditory brainstem, on top of the cochlear nucleus.

above which are the result of auditory nerve dysfunction [3]. Because this is a hereditary disease, a gene therapy should theoretically provide a fundamental cure, but the likelihood of an effective gene therapy being developed in the foreseeable future is extremely low, so other clinical modalities for restoring auditory function in these patients are urgently required.

Auditory brainstem implants have reached the clinical trial stage in Europe and the United States [1, 3, 4]. Satisfactory outcomes have been demonstrated in successful cases, bringing great hope to these patients. However, the success rate has been less than satisfactory [5-7], and various problems urgently need to be solved so that these devices can be put to effective clinical use in Japan.

The reasons that ABI, which also use electrical impulses to medically restore auditory function, have a poorer record of success than cochlear implants may be summarized as follows.

1. ABI stimulate the cochlear nucleus by means of a surface electrode (Fig. 1), but because of side effects, the actual number of electrodes that can be used is limited.
2. The tonotopic organization of the cochlear nucleus is considerably more complex than that of the cochlea.
3. In the case of cochlear implants, electrodes are inserted into the scala tympani; in ABI, however, it is often impossible to identify the optimal site for electrode implantation on the basis of anatomical criteria alone. As a result, inter-operative electrophysiological mapping is generally used to determine the implant site [8]. However, the devices presently in clinical use feature inter-electrode distance of several mm or more (Fig. 2), so the level of precision is inadequate.

Attention has been focused on trying to improve the results of ABI by using needle electrodes to stimulate deeper portions of the brainstem [9], but for this method to be successful, it will be necessary to map the cochlear nucleus with greater accuracy.

To achieve this, a multi-channel surface microelectrode was employed in the present study to measure electrical evoked auditory responses, and these responses were utilized to map the cochlear nucleus in an animal model.

In actual ABI surgery, two of the four electrodes on the probe are stimulated arbitrarily and the auditory brainstem response is recorded. The probe is 5 mm long and 3 mm wide

2. Methods

Animals used were guinea pigs weighing 250-500g. After anesthetization of the animals (intramuscularly) with ketamine (60 mg/kg) and xylazine (5 mg/kg), a click stimulus was used to measure the auditory evoked brainstem response (AABR) (Neuropack μ, Nihon Kohden) in order to confirm normal auditory function.

The animals were then placed in a supine position, and an incision was made in the skin behind the ear to expose and remove the skull to allow cerebellar retraction and subsequent visualization of the cochlear nucleus. The custom-made 64-channel microelectrode (MED64 Systems) shown in Fig. 3 was placed on the surface of the cochlear nucleus. This specialized device has 64 electrodes in an area of only 0.7 mm x 0.7 mm, with the inter-electrode distance set at only 100 μm.

Of the 64 electrode channels on this microelectrode, two points were stimulated arbitrarily and the electrical evoked brainstem responses (EABR) were recorded.

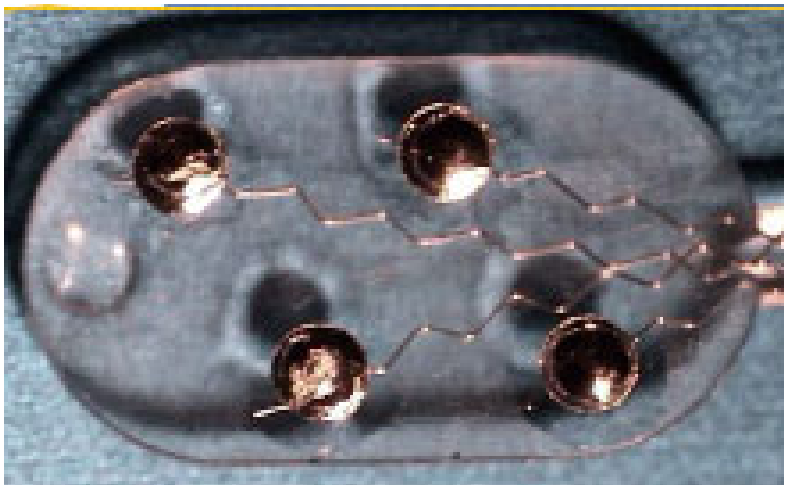


Fig. 2. Probe used clinically to determine implant site (Placing electrode: MED-EL^{R}) Dimensions: 5.5 mm x 3 mm x 0.6mm (thickness); number of electrodes: 4. Before actually placing the permanent stimulation electrode, EABR response is examined using this test electrode to confirm the best electrophysiologically controlled electrode position.

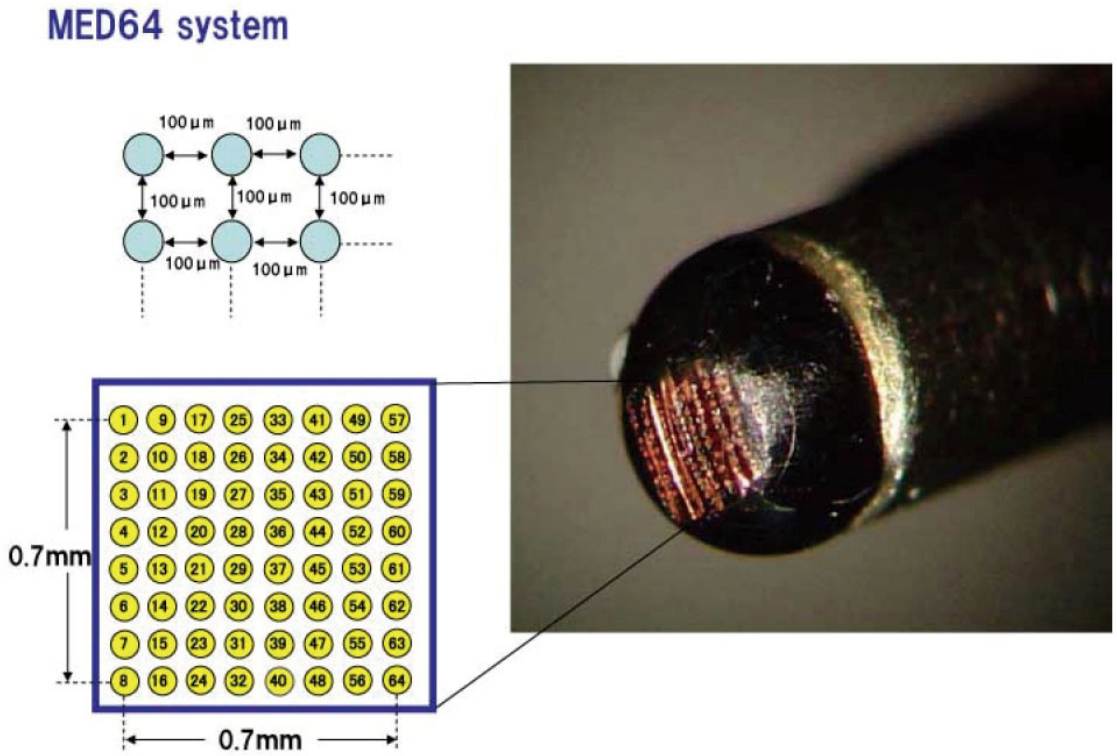


Fig. 3. 64-channel microelectrode system (MED64)
Size: 0.7 mm x 0.7 mm; inter-electrode distance: 100 µm; number of electrodes: 64.
(See text for further details)

In order to record the EABR, the active electrodes were placed on the surface of the auditory region, and the reference electrodes, consisting of stainless steel needles, were placed behind the ear. EABR were recorded using the same type of system as for AABR (Neuropack µ, Nihon-Kohden) under the following measurement conditions: number of average, 100 times; low cut filter, 1000 Hz; high cut filter, 3000 Hz.

As regards the electrical stimuli, a SEN-3041 pulse generator (Nihon Kohden) and SS-203J Isolator were used to generate bipolar pulses of 80 µsec in duration.

3. Results

3.1. EABR waveform recording system

Using the prototype 64-channel system, in which the inter-electrode distance between the two stimulating microelectrodes was 100 µm, we succeeded in recording reproducible EABR when the cochlear nucleus was stimulated electrically. Representative EABR waveforms after typical electrical stimulation of the cochlear nucleus are shown in Fig. 4.

In the case of acoustically evoked responses (AABR), 5-6 voltage deflections (wave peaks) are recorded, but in AABR generated by electrical stimulation of the cochlear nucleus, the peaks show individual variability. In humans, 1-4 peaks have been reported [5].

There are various theories about the origin of these waveforms; however, it is considered that wave I is related to the ipsilateral cochlear nerves, wave II is related to the ipsilateral cochlear nucleus, and wave III is related to the contralateral superior olive nucleus [6]. In EABR, wave II can not be observed as a result of an artifact generated by the electrical stimulation, therefore the auditory brainstem response to electrical stimulation of the cochlear nucleus is thought to appear after wave III.

In the present study also, the waves III through V were typically recorded after the artifact generated by the electrical stimulation process (Fig. 4).

These latter waveforms disappeared after the animals were sacrificed, confirming that they were not electrical artifacts.

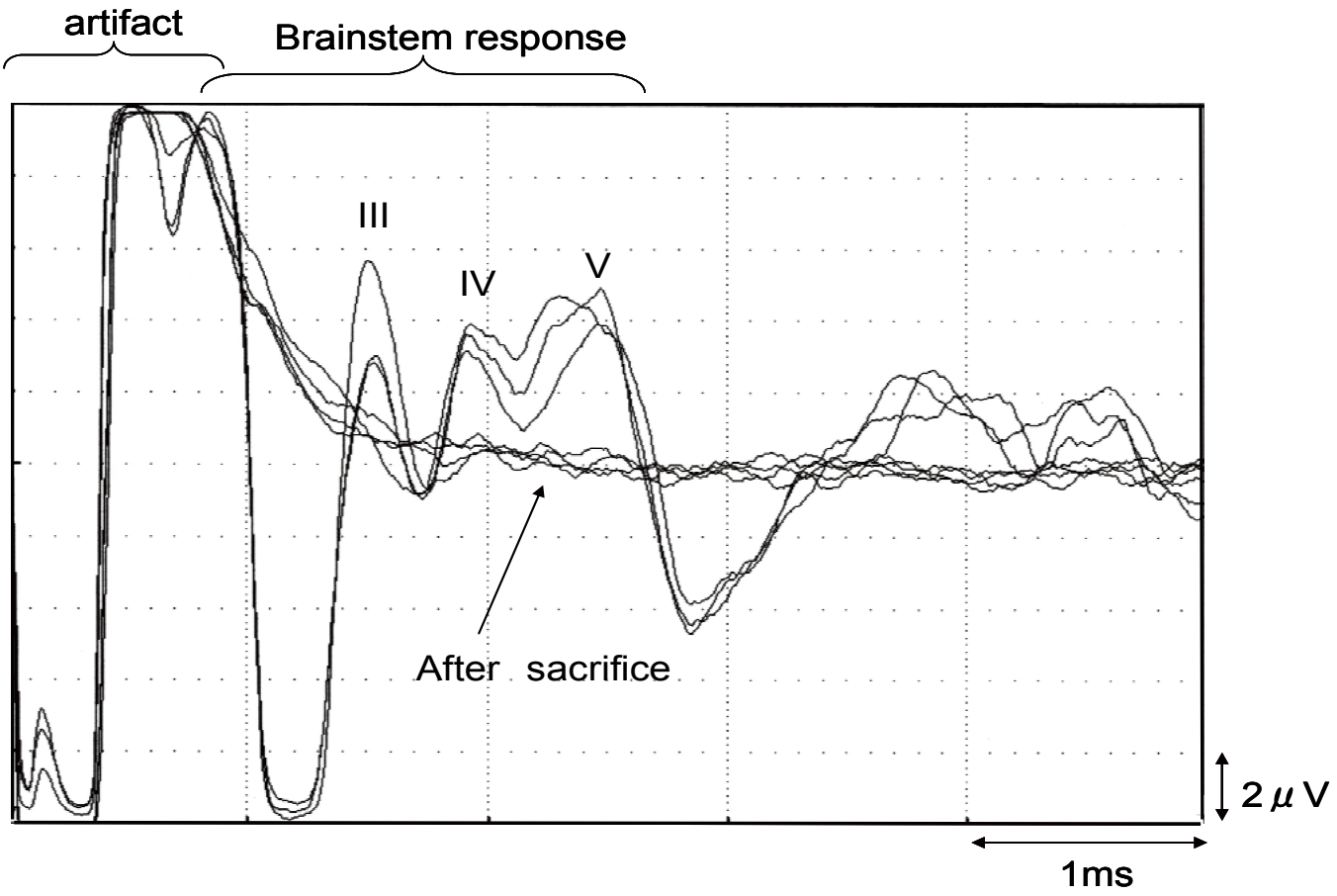


Fig. 4. Representative EABR waveforms.
Following the artifact generated by the electrical stimulation process, waveforms were recorded which were considered to be equivalent to waves III, IV, and V seen in auditory evoked brainstem responses. These latter waveforms disappeared after the animals were sacrificed, clearly confirming that they were not electrical artifacts.

3.2. EABR input/output characteristics

Figure 5 shows the input/output characteristics of wave III of the EABR in two representative cases.

In nearly all cases, the threshold value of the EABR waveform was 200-300 μA, as shown in these two cases. Saturation gradually occurred after 1000 μA

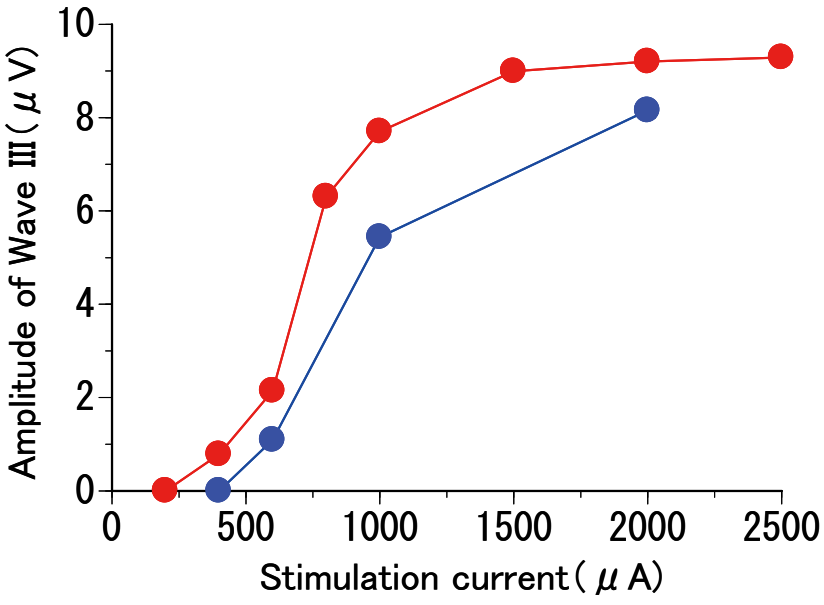
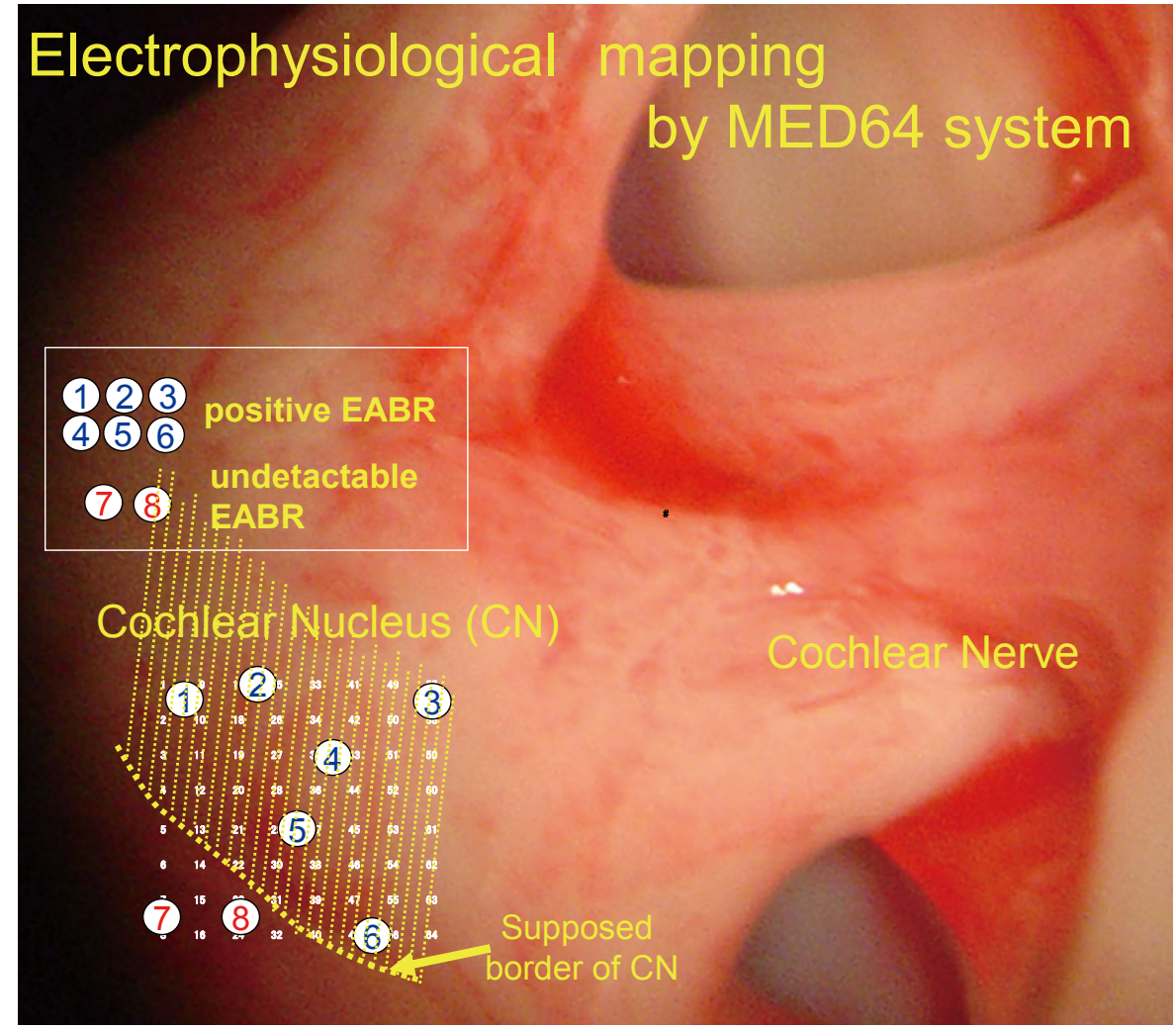


Fig. 5. Input/output functions of the wave III of the EABR in two representative cases.
The level of stimulation current is shown on the horizontal axis, while wave III amplitude is shown on the vertical axis.



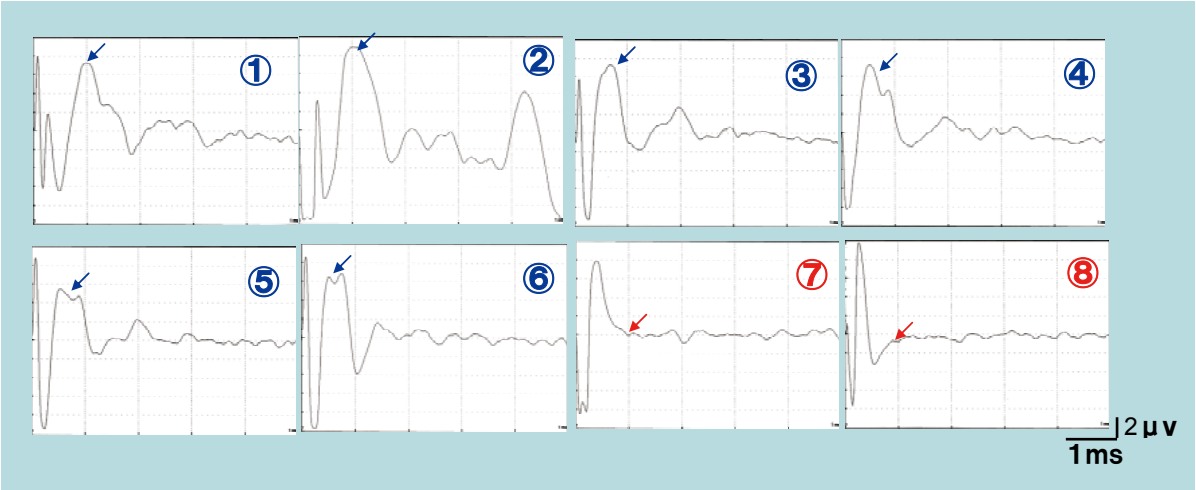


Fig. 6. Electrophysiological mapping of the cochlear nucleus using the MED64 system.
Numbers in the top figure indicate locations where bipolar stimulation was applied. The EABR recorded after electrical stimulation at each of these points are shown at the bottom. The dotted yellow lines mark the estimated borders of the cochlear nucleus based on these recordings. (See text for further details)

3.3. Electrophysiological mapping of the cochlear nucleus using the 64-channel microelectrode system

The above experiments demonstrated that this system was capable of recording EABR with excellent reproducibility. Therefore, we next attempted to use this system to perform electrophysiological mapping of the cochlear nucleus.

Mapping is considered to be most effective when the stimulation used is capable of recording reproducible waveforms with high sensitivity and an excellent S/N. Therefore, after taking into consideration the I/O characteristics of the EABR shown in Fig. 5, electrical stimulation from the dynamic portion of the signal (600 μA -1000 μA) was, for the most experiments, used to carry out the mapping.

Figure 6 shows the results of mapping of the cochlear nucleus using representative EABR. In this case, the MED64 microelectrode was placed on top of the cochlear nucleus and bipolar stimulation was performed at locations 1-8 indicated in Fig. 6. Examination of the waveforms obtained for each of these locations shows that EABR waveforms were recorded at locations 1-6 (blue arrows), while no clear EABR waveforms were recorded at sites 7 and 8 (red arrows). The dotted yellow lines in the figure indicate the estimated boundary of the cochlear nucleus according to the recorded waveforms.

Moreover, although a closer examination of the EABR waveforms recorded at stimulation points 1-6 shows considerable variation in shape and latency, there were also clear similarities between EABR waveforms from points that were relatively close to one another (stimulation at points 1-3 produced EABR waveforms with a single peak, while stimulation at points 4-6 produced a bimodal peak; however, of the EABR with a single peak, compared with points 1 and 2, the latency time at point 3 was shorter. On the other hand, the latency between peaks in the bimodal EABR resembles that at points 1-2, and the waveform latency at point 3).

Figure 7 shows the mapping results in another case. The figure shows the stimulation points and indicates whether or not an EABR waveform was recorded at each of those points.

Figure 7 does not include the actual waveforms, but as was the case in Fig. 6, waveforms from stimulation points that were located relatively close together tended to have similar characteristics, and positive and negative EABR waveforms could be clearly distinguished.

On the other hand, Fig. 8 is an example of a case where mapping was affected by blood vessels on the surface of the cochlear nucleus.

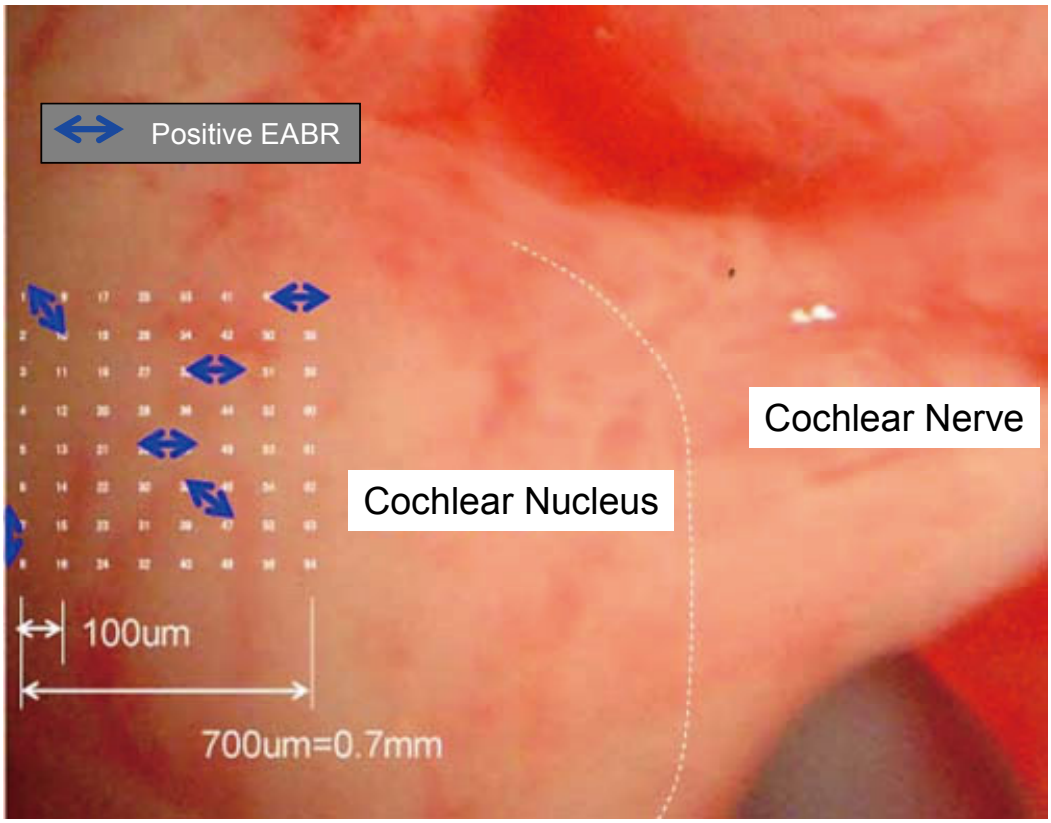


Fig. 7. Results of electrophysiological mapping of the cochlear nucleus by MED64 system (Case 2). The arrows indicate the electrode combination used for the bipolar stimulation. Blue arrows show the stimulation points at which EABR waveforms were recorded. In this case, EABR waveforms were obtained from each stimulation point. The recorded points were shifted slightly forward as compared with those in Fig. 6.

In this case, when the 64-channel microelectrode was placed on the portion of the cochlear nucleus where the blood vessels were present and electrical stimulation was applied, EABR threshold values rose at those points corresponding to the location of the blood vessels (i.e., waveforms could not be recorded at these locations at the same level of stimulation).

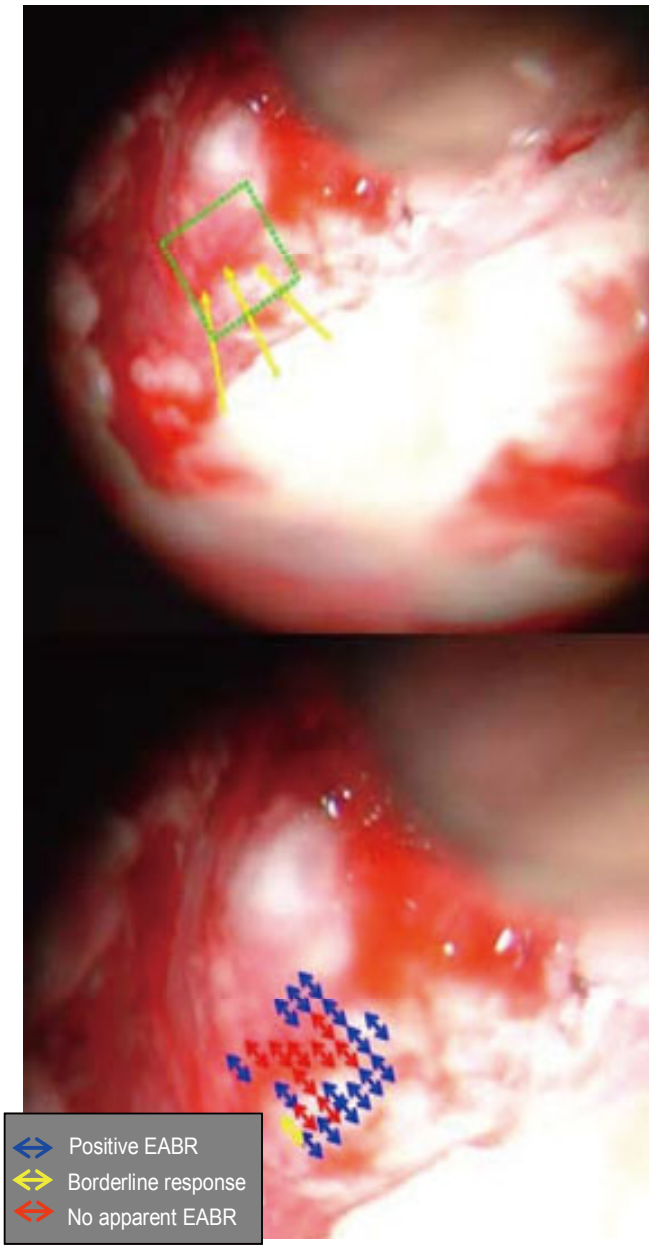


Fig. 8. A case where mapping was affected by blood vessels on the surface of the cochlear nucleus. In this case, blood vessels were observed on the surface of the cochlear nucleus (yellow arrows in Fig. 8A). When the 64-channel microelectrode was placed on the portion of the cochlear nucleus where the blood vessels were present and the same level of stimulation was applied, EABR waveforms were not recorded at locations that closely matched the position of the blood vessels (red arrows in Fig. 8B).

The results of electrophysiological mapping of the cochlear nucleus with this microelectrode system can be summarized as follows.

1. EABR waveforms were generated by 100-μA bipolar stimulation with excellent reproducibility.
2. In nearly all cases, the boundary between stimulation points that generated EABR waveforms and those that failed to generate EABR waveforms could be clearly distinguished (when the 100-μm stimulation points were shifted to the borderline region, EABR waveforms were no longer recorded).
3. Results can sometimes be affected by surface conditions where the electrical stimulation is applied (Fig. 8), and this must be taken into account when interpreting the results.

4. Discussion

The effectiveness of cochlear implants among patients with profound deafness due to sensorineural hearing loss has been well established. Cochlear implants function by electrically stimulating the cochlea. By applying electrical stimulation according to the tonotopic organization of the cochlea, the implants attempt to reproduce the pattern of nerve stimulation that occurs in the normal cochlea [2].

However, cochlear implants are not effective in the case of patients with severe hearing loss due to auditory nerve dysfunction, and it was for this reason that the auditory brainstem implants (ABI), which are designed to provide electrical stimulation directly to the cochlear nucleus, were developed. The basic structure of auditory brainstem implants is the same as that of cochlear implants, except that in the case of cochlear implants, a string-shaped electrode is implanted into the cochlea, whereas in ABI a sheet or dish-shaped electrode is placed on the surface of the cochlear nucleus, which is located in the brainstem [1-3].

Because the cochlear nucleus also has a tonotopic organization in which different cells respond to different frequencies, each stimulating electrode can be used to identify a separate pitch, and the idea is to apply this property to transmit speech-related data. However, whereas in the cochlea the tonotopic organization forms a continuous, regular arrangement following the curvature of the cochlea from the base toward the apical turn, the tonotopic organization in the cochlear nucleus is three-dimensional with a branched and laminated arrangement (Fig. 9).

The regular arrangement of neurons within the auditory pathway in pitch order, from low to high, is referred to as tonotopic organization. In the cochlear nucleus the characteristic frequency of the neurons is arranged so that the pitch order goes from high to low as one moves from the dorsal nucleus to the ventral nucleus [10,11].

As a result, with this type of tonotopic organization there is a limit to the precision with which stimulation

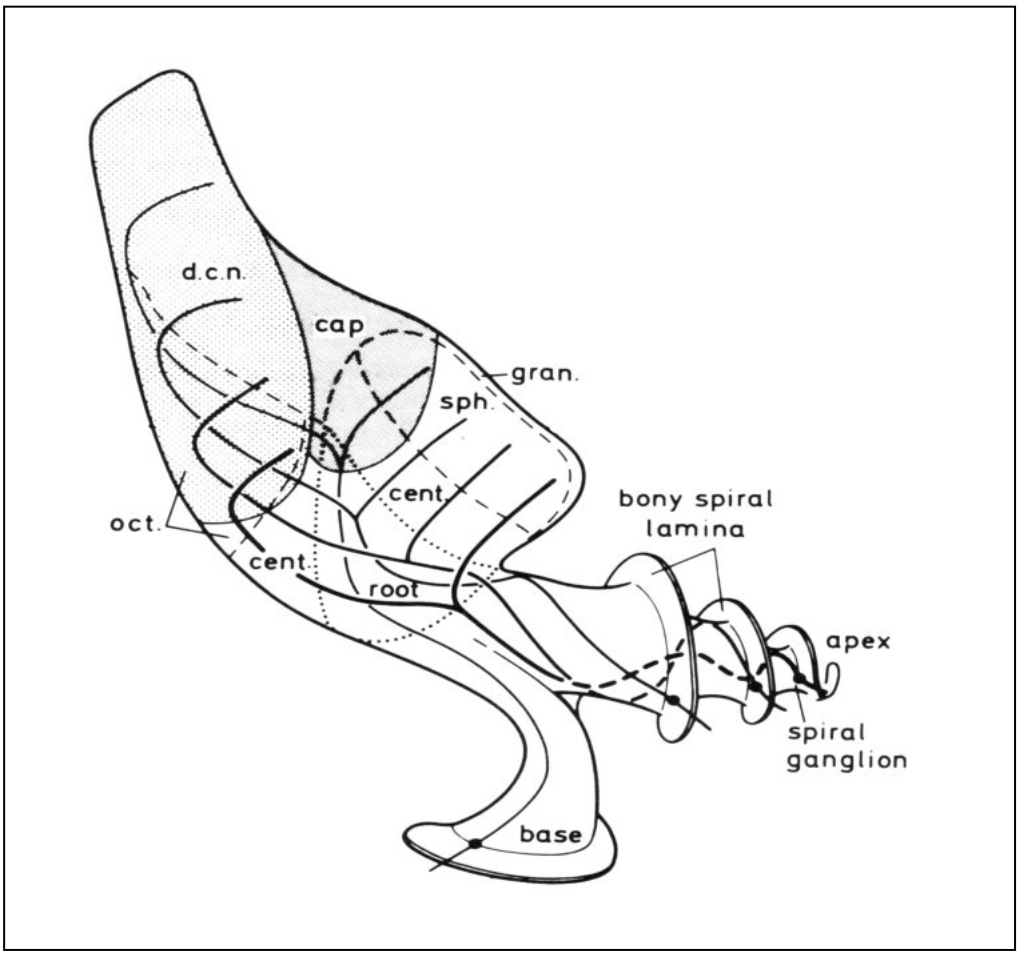


Fig. 9. Direction of cochlear nerves in the cat cochlear nucleus (modified from Moore and Osen, 1979 [10])
Anatomically the cochlear nucleus is divided into the dorsal and ventral cochlear nuclei. The ventral nucleus is further subdivided into anterior and posterior nuclei. The primary auditory nerve branches from the cochlear nucleus, with the ascending branch connecting to the anterior nucleus, and the descending branch traveling from the posterior nucleus to its termination in the dorsal nucleus.

can be applied for each frequency with the types of ABI surface electrodes presently in use. To solve this problem, a method has been developed that involves insertion of a microelectrode to provide deep brain stimulation [12-18].

Furthermore, deep brain stimulation electrodes can be fixed in place with greater stability, and this is expected to facilitate improved auditory function.

In the present study, EABR were recorded using a surface microelectrode with an inter-electrode distance of only 100 μm, which is less than one tenth the electrode separation of the electrode devices presently in clinical use. These same microelectrodes were used to conduct mapping of the cochlear nucleus and found that the electrophysiological boundaries could be identified quite clearly with this method.

The clinical significance of these findings can be summarized as follows:

Usefulness in mapping the cochlear nucleus

Whether in conventional ABI, or in any microelectrode-type ABI that might come into use in future, to further improve results for auditory comprehension of spoken language it is essential that the mapping of cochlear nucleus can be performed as precise as possible.

In the experimental stage of the present study, a 0.7 x 0.7 mm electrode array was used. In theory, the results of electrophysiological mapping should improve as the distance between electrodes becomes smaller and as the number of stimulation points increases. However, considering that the size of the cochlear nucleus in humans is about 8 mm x 3.5 mm, further study will be necessary to determine the optimal electrode configuration (electrode number, inter-electrode distance, etc.) for use in the clinical setting.

As shown in Fig. 8, results were negative when blood vessels were present. Therefore, we consider that in order to identify the complete perimeter of the cochlear

nucleus, it will be necessary to use a larger stimulating electrode, one that is sufficiently large to cover the entire cochlear nucleus.

In addition, the present study demonstrated that the EABR-positive boundary could be distinguished relatively clearly by means of electrophysiological mapping; however, the relation between this boundary and the actual anatomical boundary remains unclear. In actual ABI, it is sufficient to simply determine the presence or absence of an evoked reaction, but in the future we need to clarify the relation between the electrophysiological boundary and the anatomical boundary.

Usefulness as the stimulating electrode in ABI

In the present study, bipolar stimulation with an inter-electrode distance of 100 μm was capable of adequately recording EABR. Furthermore, following very slight shifts in the stimulation region, the EABR suddenly disappeared or the shape of the waveforms changed, indicating that the microelectrode used was capable of applying relatively localized electrical stimulation.

These results indicate that the use of a microelectrode as the stimulating electrode in ABI may make it possible to achieve a more precise discrimination of pitch, although previous works have indicated that a penetrating type stimulation electrode is more efficient than a surface electrode in terms of accessing the tonotopic organization of the cochlear nucleus [12-18].

The main purpose of the present study was to evaluate the usefulness of this multi-channel surface microelectrode in mapping the cochlear nucleus, so the EABRs in response to the electrical stimulation of the cochlear nucleus were evaluated. In future, by measuring (or assessing) the frequency response of the auditory cortex in response to the electrical stimulation of the cochlear nucleus, it should be possible to specifically assess the frequency discrimination of the narrow bipolar stimulation.

4. Summary

The unequivocal EABR can be elicited by the bipolar stimulation with very short separation (inter-electrode distance = 100 μ m).

Preliminary results of electrophysiological mapping using the MED 64 system indicated that more precise electro-physiological mapping may be possible based on the EABR threshold distribution using bipolar stimulation with this very short separation.

The multi-channel surface microelectrode expected to be usefully applied in the clinical use in the electrophysiological mapping to determine the optimal location for the positioning of the ABI.

Acknowledgements

This study was supported by a grant-in-aid from the Japanese Ministry of Education, Culture, Sports, Science and Technology for fiscal 2006-2007 and Tohoku University Global COE Program ”Global Nano-Biomedical Engineering Network Centre”.

5. References

[1] Jackson KB, Mark G, Helms J, Mueller J, and Behr R. An auditory brainstem implant system. *Am J Audiol* **11**, 128-133, 2002.

[2] Clark G. Cochler implant –fundmentals and applications. Springer, 2003.

[3] hochmair E, Belr R, and Mueller J. Auditory brainstem implants using high rate multichannel pulsatile stimulation. *Otol Jpn* **10**, 559-569, 2000.

[4] Colletti V. Auditory outcomes in tumor vs. Nontumor patients fitted with auditory brainstem implants. *Adv Otorhinolaryngol* **64**, 167-85, 2006.

[5] Otto SR, Brackmann DE, Hitselberger WE, Shannon RV, and Kuchta J. Multichannel auditory brainstem implant: update on performance in 61 patients. *J Neurosurg* **96**, 1063-71, 2002.

[6] Nevison B, Laszig R, Sollmann WP, Lenarz T, Sterkers O, Ramsden R, Fraysse B, Manrique M, Rask-Andersen H, Garcia-Ibanez E, Colletti V, and von Wallenberg E. Results from a European clinical investigation of the Nucleus multichannel auditory brainstem implant. *Ear Hear* **23**, 170-183, 2002.

[7] Behr R, Muller J, Shehata-Dieler W, Schlake H-P, Helms J, Roosen K, Klug N, Holper BM, and Lorens R. The High rate CIS auditory brainstem implant for restoration of hearing in NF-2 patients. *Skull Base* **17**, 91-108, 2007.

[8] Nevison B. A guide to the positioning of brainstem implants using intraoperative electrical auditory brainstem responses. *Adv Otorhinolaryngol* **64**, 154-66, 2006.

[9] Liu X, McPhee G, Seldon HL, and Clark GM. Histological and physiological effects of the central auditory prosthesis: surface versus penetrating electrodes. *Hear Res* **114**, 264-274, 1997.

[10] Moore JK and Osen KK. The human cochlear nuclei. *Exp Brain Res* (Suppl II), 36-44, 1979.

[11] Moore JK. Cochlear Nuclei: Relationship to the auditory nerve. In: *Neurobiology of Hearing: Cochlea*, edited by Altschuler RA, Hoffman DW, Bobbin RP, Raven Press, New York, NY, 283-301, 1986.

[12] Otto SR, Brackmann DE, Hitselberger WE, et al. Brainstem electronic implants for bilateral anacusis following surgical removal of cerebellopontine angle lesion. *Otolaryngol Clin North Am* **34**, 485-499, 2001.

[13] McCreery DB, Shannon RV, Moore JK, and Chatterjee M. Accessing the tonotopic organization of the ventral cochlear nucleus by intranuclear microstimulation. *IEEE Trans Rehabil Eng* **6**, 391-399, 1998.

[14] Evans DA, Niparko JK, Altschuler RA, Frey KA, and Miller JM. Demonstration of prosthetic activation of central auditory pathways using [14C]-2-deoxyglucose. *Laryngoscope* **100**, 128-137, 1990.

[15] el-Kashlan HK, Niparko JK, Altschuler RA, and Miller JM. Direct electrical stimulation of the cochlear nucleus: surface vs. penetrating stimulation. *Otolaryngol Head Neck Surg* **105**, 533-543, 1991.
[16] Rosahl SK, Mark G, Herzog M, Pantazis C, Gharabaghi F, Matthies C, Brinker T, and Samii M. Far-field responses to stimulation of the cochlear nucleus by microsurgically placed penetrating and surface electrodes in the cat. *J Neurosurg* **95**, 845-852, 2001.
[17] El-kashlan HK. Multichannel cochlear nucleus stimulation. *Otolaryngol Head Neck Surg* **121**, 169-175, 1999.
[18] Takahashi H, Nakao M, and Kaga K. Accessing ampli-tonotopic organization of rat auditory cortex by microstimulation of cochlear nucleus. *IEEE Trans Biomed Eng* **52**, 1333-1344, 2005.