이학박사 학위논문

Promontory Electrically Evoked Auditory Brainstem Response for Perioperative Evaluation of Auditory Function in Cochlear Implant

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Abstract

Promontory Electrically Evoked Auditory Brainstem Response for Perioperative Evaluation of Auditory Function in Cochlear Implant

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Introduction: A cochlear implant is a hearing rehabilitation device for moderate to severe sensorineural hearing loss who cannot hear the sound even with a hearing aid. This device restores hearing by directly stimulating the auditory nerve with electrical stimulation containing sound information by implanting electrodes into the cochlea of the deaf person. To predict the clinical outcome after cochlear implant surgery, it is imperative to check the auditory function of the deaf person before surgery. Although the usefulness of observing evoked responses by promontory

stimulation to evaluate the auditory function has been known through previous studies, it is rarely used clinically due to lack of reliability, difficulty in identifying stimulation locations, and limited stimulation range by single-channel electrodes. In this study, the necessity of auditory function evaluation through multichannel stimulation of the promontory was confirmed by observing whether there was a change in the characteristics of the evoked potential by stimulation of the auditory nerve according to the change in the stimulation position of the promontory.

Methods: A surface-type multichannel electrode suitable for placement on the promontory of an animal was designed, and a neural stimulator that outputs electrical stimulation was developed. For four normal hearing (NH) and four deaf animals, install multichannel electrodes on the promontory so that channel A(Ch-A) is located near the apex of the cochlea and channel B(Ch-B) is located near the base. MicroCT imaging was performed to confirm the electrode positions. Electrically evoked auditory brainstem response (EABR) induced by promontory stimulation was measured using the two electrode channels. The amplitude growth function (AGF), slope, and latency of wave V of EABR were analyzed. The density of spiral ganglion neurons (SGNs) contributing to auditory system activity by electrical stimulation through histology of the

cochlea with NH and deafness was also compared.

Results: It was confirmed by microCT scans that the electrode is positioned in the correct position on the promontory in 2 out of 3 animals in the NH group and 1 out of 2 in the deaf group. In the case of AGF, in subjects whose electrode positions were confirmed, there were many sections with greater amplitude and steeper slope during Ch-A stimulation than during Ch-B stimulation in both groups. The amplitude was significantly greater in the NH group than in the deaf group in Ch-B. The slope showed steeper in Ch-A than Ch-B in both groups. The range of stimulus intensities that EABR was observed was more comprehensive with Ch-B than Ch-A. The latency was significantly shorter with Ch-A than with Ch-B, regardless of hearing. In Ch-B, the latency of the NH group was shorter than that of the deaf group. The Ch-A stimulation of the NH group was significantly shorter than the Ch-B stimulation of the deaf group. There was no significant difference in the threshold. The density of SGN was about 2.9 times higher in the NH group than in the deaf group.

Conclusion: The neural stimulation device and surface-type multichannel electrode suitable for electrical stimulation of the promontory in animals were developed, and the properties of the EABR with two channels in the normal hearing and deaf subjects

were compared. It was confirmed that there were differences in characteristics of AGF, slope, and latency of EABR obtained by stimulating two channels to stimulate different positions of the promontory. This may be due to the characteristics of current spread, and the number and distribution of stimulated SGNs are reflected according to the physical location of the electrode. So, using multichannel electrodes is necessary for promontory stimulation for auditory function evaluation in clinical practice. However, there are cases where the electrode was fixed in an unintended position, so it is needed to improve the electrode design and fixation method and monitor the condition of the electrode-tissue interface after installation. In addition, it is necessary to observe the characteristics of the auditory nerve response that stimulated various positions of the promontory in the partial hearing loss model with the various distribution of spiral ganglion neurons. Through this, the auditory function of a person with hearing loss can be objectively evaluated. It is expected to be used as a perioperative prognostic factor in a cochlear implant.

Keyword : Cochlear implant, evaluation of auditory function, promontory stimulation, multichannel electrode, electrically evoked auditory brainstem response, perioperative, prognostic factor
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List of Abbreviations

Abbreviation	Term
ABR	Auditory brainstem response
AGF	Amplitude growth function
ASSR	Auditory steady state evoked potential
CI	Cochlear implant
CT	Computed tomography
EABR	Electrically evoked auditory brainstem response
ECAP	Electrically evoked compound action potential
eV	Wave V of EABR
NH	Normal hearing

PBS	Phosphate buffered saline
SGN	Spiral ganglion neuron

Chapter 1. Introduction

1.1. Study Background

A cochlear implant is a hearing rehabilitation device for people with moderate to severe sensorineural hearing loss who do not have any benefit even using a hearing aid. This device restores hearing by directly stimulating auditory cells with electrical stimulation containing sound information after implanting electrodes into the cochlea of the deaf person through surgery [1, 2].

Before cochlear implant surgery, tests for auditory function evaluation and prediction of clinical outcomes are required. There are mainly subjective tests and objective tests. The subjective test evaluates hearing in response to stimulation with the cooperation of the patient, and the objective test evaluates hearing by the response of the nervous system regardless of the patient's intention [3, 4]. Objective tests include behavioral audiometry, visual reinforcement audiometry, impedance audiometry, auditory brainstem response (ABR), auditory brainstem response audiometry (ASSR), and otoacoustic emission test, and subjective tests include pure tone audiometry and speech perception test [3, 5]. In addition, medical

imaging, psychological and neurological examination are performed to select cochlear implant operators [1, 2].

Among the objective tests, the ABR test is the most used for hearing tests of a person with hearing loss. It is used to measure the brainstem response after click sound or tone sound stimulation. [3, 5, 6]. Through medical imaging such as CT or MRI, the shape of the inner ear, the presence or thickness of the auditory nerve, and other factors such as ear inflammation or other abnormalities are checked, and whether the cochlear implant can be used well [3, 7]. Among the subjective tests, pure tone audiometry is a basic hearing test that listens to pure tones of various frequencies and checks the threshold, and the speech perception test plays syllables, words, or sentences and checks how much one listens [3, 8].

Cochlear implant surgery is performed in consideration of the test results, the cause of hearing loss, the timing of hearing loss, and the duration of hearing loss [3, 9]. However, there is significant individual variation in the results of cochlear implant rehabilitation [10, 11]. A few reasons have been pointed out. Peripherally, it is the survival and distribution of auditory nerve cells required to generate action potentials in response to electrical stimulation [12, 13]. There is a retroauricular lesion with a problem in the pathway that transmits the activation signal of the auditory nerve cell to the

auditory cortex as an auditory pathway problem [14, 15]. And plastic changes in the central auditory system, including the subcortical nervous system from the cerebral cortex, and higher cognitive functions such as learning, memory, and attention [10, 11, 16-18].

Since the cochlear implant restores hearing by directly electrically stimulating the auditory nerve through an electrode inserted into the cochlea, it is difficult to expect the results of cochlear implant rehabilitation if the auditory nerve activation fails when the auditory nerve is electrically stimulated. Therefore, whether the stimulated nerve is activated is one of the most important considerations in the decision of cochlear implant surgery [19-21].

As an objective test to check whether the auditory nerve is normal, there are MR imaging and electrical stimulation evoked response tests. The presence of the auditory nerve can be confirmed through MR imaging, the thickness of the vestibulocochlear nerve and the ratio of the facial nerve can be checked, and the condition of the auditory nerve can be confirmed, and the result of cochlear implant rehabilitation can be predicted [4, 7]. The electrical stimulation evoked response observation is an objective test to evaluate the function of the auditory nerve. After

cochlear implant surgery, there are tests such as electrically compound action potential, which is the response of the auditory ganglion, and the electrically evoked auditory brainstem response, which is the brainstem response, using implanted electrodes. Before cochlear implant surgery, electrodes are not implanted in the cochlea, so electrodes for electrical stimulation must be installed. There is a promontory stimulation test (Fig. 1) that stimulates the auditory nerve by fixing the electrodes to a promontory or round window niche. Some researchers suggested that the promontory stimulation test for sensorineural hearing loss could be a useful clinical tool for selecting cochlear implant patients by confirming the auditory nerve status [22, 23]. However, it is rarely used clinically due to difficulties in confirming the location of promontory stimulation, lack of reliability of results, limited stimulation range due to single-channel electrodes, and low correlation with cochlear implant rehabilitation results [24, 25].

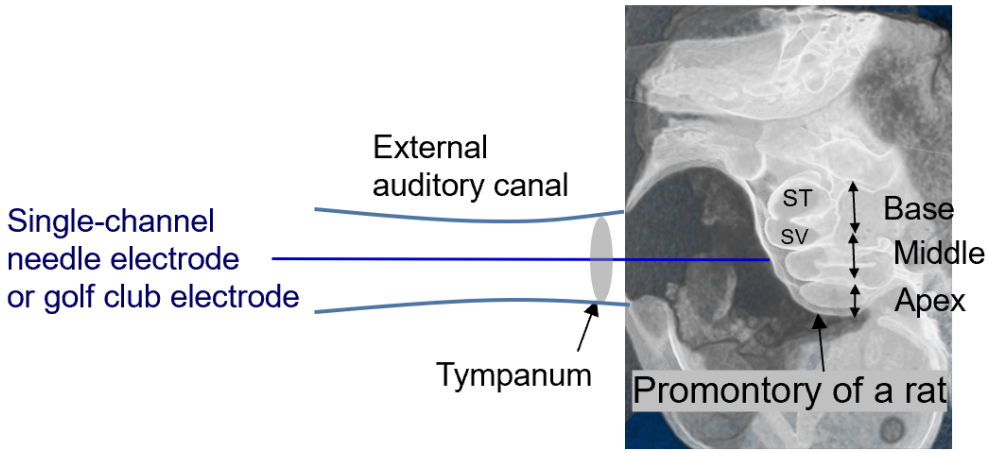


Figure 1. Promontory stimulation with single-channel electrode

In some studies, electrically compounding action potential (ECAP), electrically evoked auditory brainstem response (EABR), etc., were measured and suggested that it could be used to predict the prognosis of cochlear implant surgery [19, 26, 27]. ECAP is a peripheral auditory nerve response that can be obtained by stimulating spiral ganglion neurons (SGN) and is related to SGN density [28, 29]. However, the association with cochlear implant prognosis is poor [24, 30]. Because ECAP is a peripheral auditory response, it may be because it does not reflect neural plastic changes in the upper auditory nervous system caused by hearing loss, auditory neuropathway spectrum disorders, etc. [18, 31, 32]. When evaluating auditory function by sound stimulation, wave V of auditory brainstem response is a clinically important factor. Compared to ECAP, EABR is a brainstem response in the upper

auditory center, reflects changes in subcortical neuroplasticity or lesions, and is useful for evaluating auditory function because it is related to the prognosis of cochlear implant surgery [32, 33]. In addition, in a study measuring EABR using multichannel intracochlear electrodes, it was shown that the characteristics of EABR were different due to the influence of the spread of excitation and channel interaction depending on the stimulation mode [33-35].

To measure EABR, spiral ganglion neurons must be stimulated, and electrode positions for stimulating or measuring the induced response can be divided into extracochlea and intracochlea [23, 36, 37]. Extracochlear stimulation is performed by placing electrodes on a round window niche or promontory to stimulate the auditory nerve or measure the induced auditory nerve response. In the case of intracochlear stimulation, stimulation or measurement is performed by inserting electrodes into the cochlea through a round window approach or cochleostomy. Promontory stimulation, an EABR measurement method through extracochlear stimulation, can stimulate the auditory nerve without damaging the cochlea. In addition, the surface area is wider than the round window niche, which is advantageous for positioning multichannel electrodes, and the apex, middle, and base parts of the cochlea are separated so that a specific frequency band can be stimulated.

During cochlear implant surgery, the electrode is inserted through the round window of the cochlea or through a hole. Lymph fluid flows through the hole, and hearing loss or foreign substances such as blood or bone powder enter, fibrosis, and new bone formation.[38]. It is also known to induce programmed cell death of inner hair cells due to damage to internal structures [39]. Since electrode insertion can cause such permanent damage, it is crucial to check the condition of the deaf or hard of hearing person's auditory system before cochlear implant surgery. It can also be used to recheck the state of the auditory system before implantation of electrodes during cochlear implant surgery or to observe changes in auditory function after the procedure.

1.2. Purpose of Research

In this study, surface-type multichannel electrodes were installed on the promontory of the cochlea, and electrical stimulation was delivered to measure EABR. A neural stimulation device capable of stimulation with appropriate parameters and an electrode having a size and shape suitable for promontory stimulation were developed and used. This study tried to investigate whether

characteristics not seen with single-channel electrodes were observed or whether there was a difference in characteristics between normal hearing and hearing loss subjects (Fig. 2).

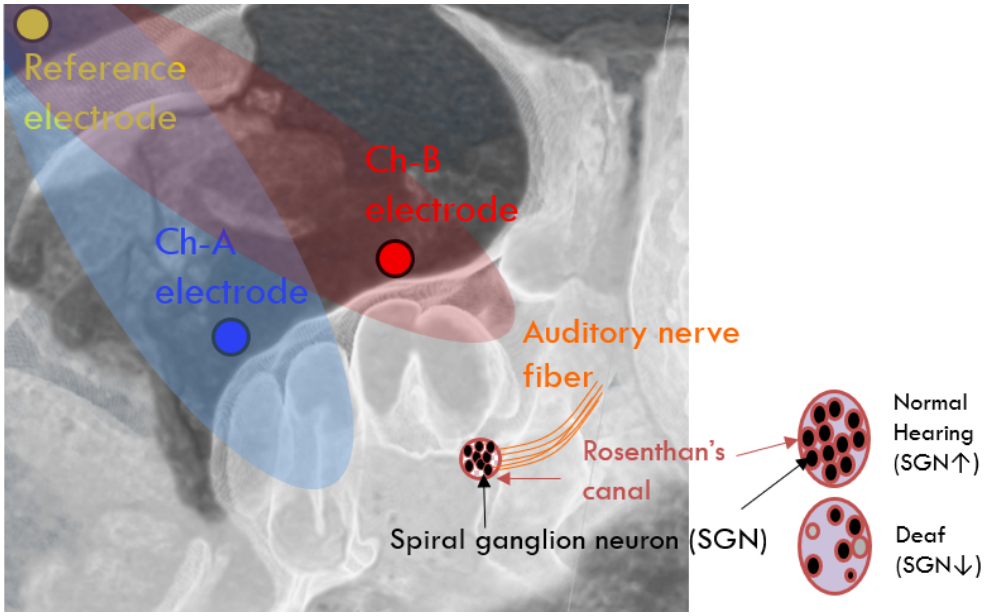


Figure 2. Conceptual figure of promontory stimulation with a multichannel electrode. Yellow, Blue, Red circles are reference, Ch-A, and Ch-B electrodes, respectively. The transparent blue and red regions are the approximate electric field for Ch-A and the reference electrode and Ch-B and reference electrode.

Chapter 2. Materials and Methods

2.1. Development of a Neural Stimulator and Electrode

2.1.1 Neural Stimulator

The neural stimulator was designed as shown in the block diagram below using the developed neural stimulation chip (TODOC Co. Ltd., Seoul, ROK) (Fig. 3). Battery power was used to generate the voltage for the circuit and stimulation. It was designed to communicate with an external user interface using the microcontroller's Bluetooth communication function so that the neural stimulation chip could be manipulated, and an external trigger output was included to inform the timing of stimulation. A biphasic current balanced pulse was output to prevent damage to nerve cells due to electrical stimulation, and a negative phase first pulse is output for efficient stimulation [40, 41]. Four channel current stimulation was possible in monopolar mode, and the pulse amplitude, width, and rate can be adjusted (Fig. 4). This stimulator was commercialized, and detailed data such as the electrical circuit schematics were not disclosed.

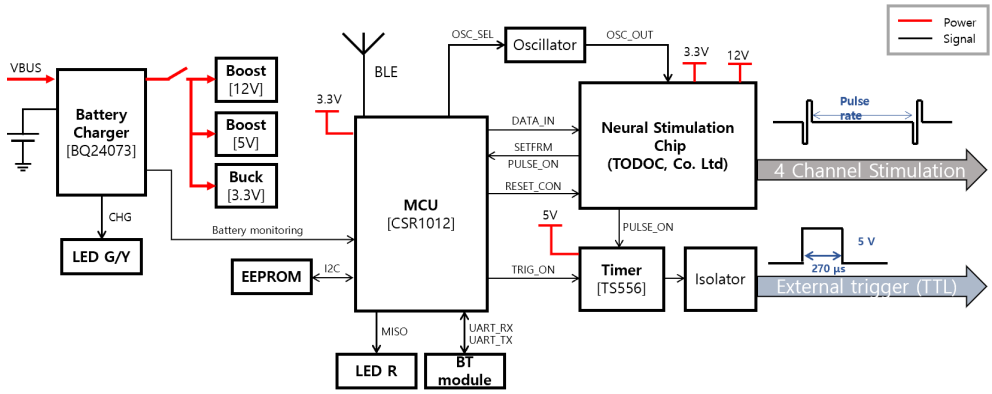


Figure 3. Block diagram of promontory stimulator

It was designed to have the setting range and adjustment resolution indicated in Table 1 for the stimulation parameters, including pulse amplitude, pulse width, and pulse rate.

Table 1. Specification of configurable parameters of the neural stimulator

Configurable Parameters (unit)	Range	Step
Pulse amplitude (㎂)	0 – 10230	10
Pulse width (㎲)	10 – 300	10
Pulse rate (Hz)	20-230	5

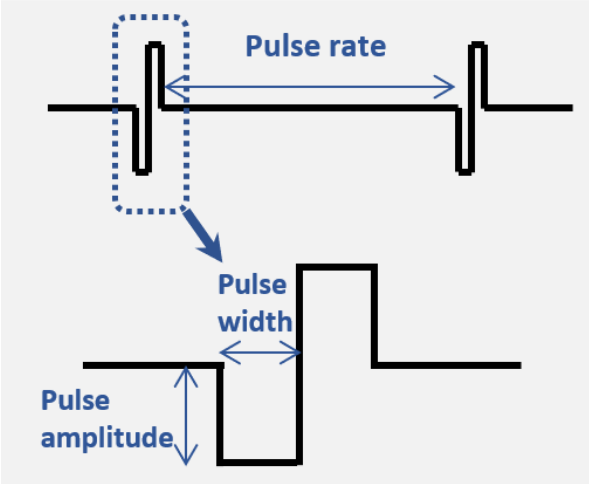


Figure 4. Configurable parameters of a stimulation pulse. The pulse amplitude is the amplitude from the baseline to the peak of the pulse. The pulse width of the negative phase is the duration from the negative edge of the pulse to the positive edge. The pulse width of the positive phase is vice versa. The pulse rate is the interval of the repetitive pulses.

2.1.2 Surface-Type Multichannel Electrode

The electrode was designed in consideration of the size of a rat cochlea [42-44]. So, it can be applied on the promontory surface, which is the bone wall of the cochlea. A surface-type electrode was designed and fabricated in consideration of the size of the cochlea (Fig. 5). With four channels of stimulation electrodes, the diameter

was 0.3 mm, the spacing between the electrodes was 0.55 mm, and the electrode impedance was set to 5 kΩ (@ 1 kHz). There was one reference electrode separately, and the diameter was Φ 0.86 mm. After attaching a Pt-Ir film on it using liquid polymer crystal as the substrate of the electrode, patterning according to the drawing through laser machining process, and coating with silicon elastomer [45, 46].

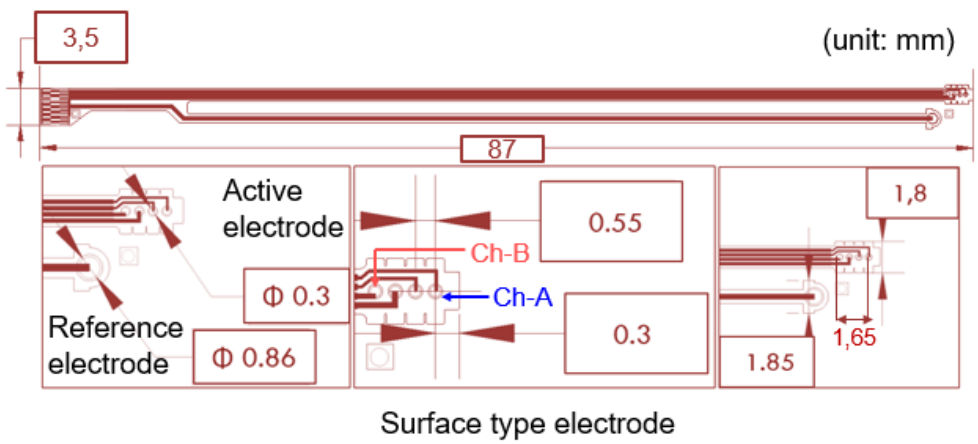


Figure 5. Design of the four channel surface-type electrode. The diameter of the active electrode and reference one was 0.3 and 0.86 mm, respectively. The interspace between channels was 0.55 mm. Two channels (Ch-A, Ch-B) were used for promontory stimulation.

2.2. Experimental Setup for EABR Recording

2.2.1. Animal Preparation

SD rats (8-27 weeks old) were used as animals and consisted of a normal hearing group (n=4) and a deaf group (n=4). Anesthetized with intramuscular injection of zoletil (30 mg/kg) and xylazine (5 mg/kg). To prevent dehydration, 2 ml of normal saline was injected subcutaneously into the back. The body temperature was maintained at 35~37° C during the experiment using a hot pad. The back of one ear was extensively shaved and disinfected. After retroauricular incision, bullotomy was performed to expose the promontory-bony wall of the cochlea [47-49]. To prevent brainstem reaction due to normal hearing, round window puncture and gentamycin (Gentamicin inj 80mg, Shin Poong Pharm. Co., Ltd., Ansan, ROK) irrigation were performed several times to create acute deaf (Fig. 6). Deaf was confirmed by ABR (≥75 dB SPL, click sound) recording (SmartEP, Intelligent Hearing Systems, FL, USA) right after deafening operation [47, 49]. The electrode was installed on the promontory, the bony wall of the animal's cochlea. The active electrode was placed on the promontory, as shown in the figure below. Ch-A is close to the cochlea apical part,

and Ch-B is close to the basal part. After the active electrode was placed on the promontory, gauze was filled in the middle ear cavity so that the electrode was in close contact with the surface of the promontory and fixed with a bond. The reference electrode was placed subcutaneously on the same side of the chin as the active electrode was installed, and saline was applied and fixed with a bond (Fig. 6) [50, 51]. All experiments were approved by the Institutional Animal Care and Use Committee in Seoul National University Hospital (SNUH-IACUC) and animals were maintained in the facility accredited AAALAC International (#001169) in accordance with Guide for the Care and Use of Laboratory Animals 8th edition, NRC (2010).

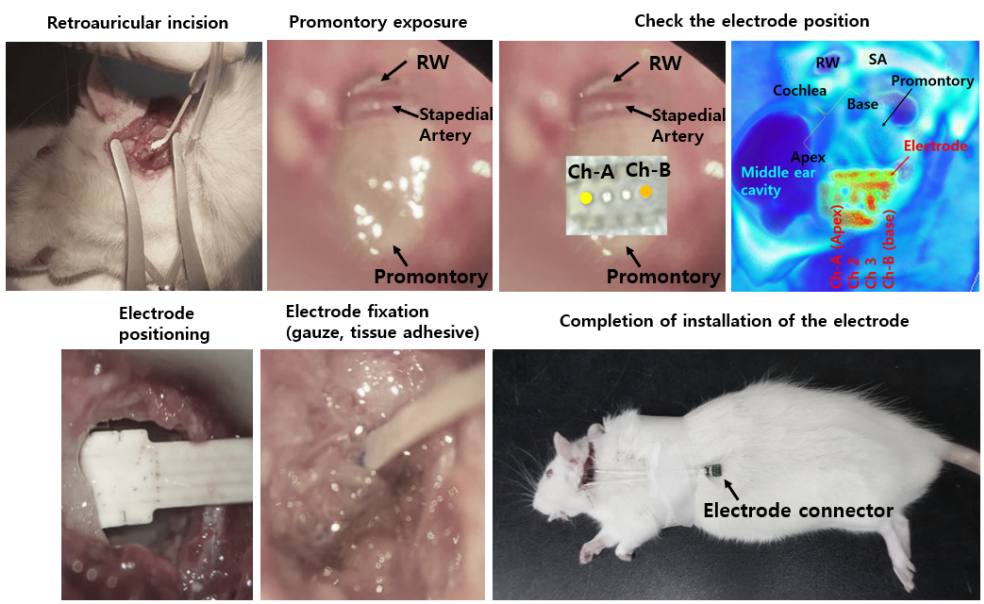


Figure 6. Procedure for installation of the electrode. It was installed, fixed on the promontory, and fixed by filling it with gauze and application of tissue adhesive.

2.2.2. Electrode Position on the Promontory

To check the position of electrode, a microCT (Quantum GX2, PerkinElmer, Waltham, MA, USA) scan was performed on some subjects. CT images were analyzed using the image processing and analysis tool ImageJ (National Institutes of Health, Bethesda, MD, USA). After reading the Dicom file, brightness/contrast was automatically optimized, and then 3D was reconstructed using a 3D volume viewer plug-in. ThermalLUT was selected for the transfer function so that the electrode and promontory were well distinguished [52, 53]. The view in which the positional relationship between the electrode and the promontory is best identified was captured, the dorsoventral, ventrodorsal, and left lateral views were confirmed (Fig. 7).

Figure 7. MicroCT scans in three projections. Dorsoventral, ventrodorsal, and left lateral view.

2.2.3. Setup for EABR Recording

Animals installed with electrodes were placed in an electrical and sound noise proof box, and electrodes were connected to measure electrical stimulation and evoked potential. To conduct electrical stimulation using Ch-A and Ch-B electrodes and observe the evoked auditory brainstem response (EABR), the promontory stimulator and the recorder (SmartEP, Intelligent hearing systems, FL, USA) with preamplifier (Opti-Amp, Intelligent hearing systems, FL, USA) were used (Fig. 8). The preamplifier provides 1K gain and 8 kHz low-pass filtering. Recording parameters were configured (100k gain, 30-3000 Hz filtering, 200 μs blanking time). EABR was acquired and averaged 1024 times as guided by the manufacturer [50]. For the recording of EABR, non-inverting, inverting, and GND

electrodes were placed on the back of the neck, retroauricular area, and a leg for evoked potential measurement, respectively [50, 51, 54]. The active and reference electrodes for stimulation were located on the promontory and chin on one side, respectively [50, 51, 54]. The pulse rate and duration were fixed at 20 Hz and 100 μs/ph, respectively. Signals were recorded while increasing the intensity of stimulation.

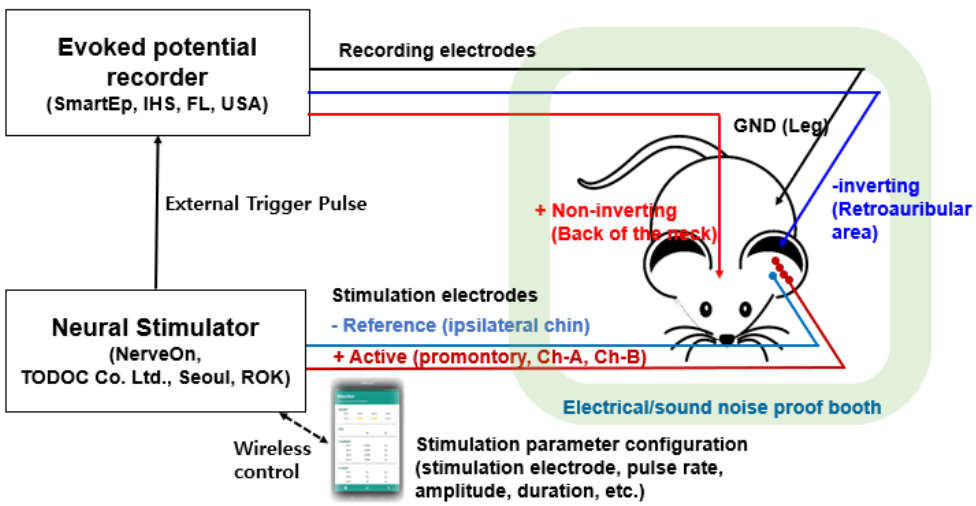


Figure 8. Experimental setup for EABR measurement. The external trigger of the neurostimulator was connected to an evoked potential recorder, and each electrode was positioned at a specific site. Stimulation parameters were controlled by an Android-based application.

2.3. Data Processing and Analyzed Parameters

The peak amplitude and latency of EABR wave V (eV) measured by applying electrical stimulation using Ch-A and Ch-B were obtained, and amplitude growth function (AGF), slope, and latency were analyzed (Fig. 9) [28, 29, 55]. The amplitude of eV is the difference between the generated peak amplitude and the amplitude of the following trough [55, 56]. Latency is the time from stimulus onset to the peak of an eV. AGF is an I/O function of the auditory nerve with a graph plotting stimulus intensity on the x-axis and eV amplitude on the y-axis [29, 55, 56]. The Slope compared the values

obtained through linear regression of all individual data of AGF of Ch-A and Ch-B in the NH and deaf groups. Signals below 0.2 μVpp, the noise floor observed in the absence of stimulation, were excluded from the analysis (Fig. 10) [29, 55, 56]. Signals were excluded for analysis difficult to observe due to a facial nerve or myogenic response (Fig. 11) [50, 56].

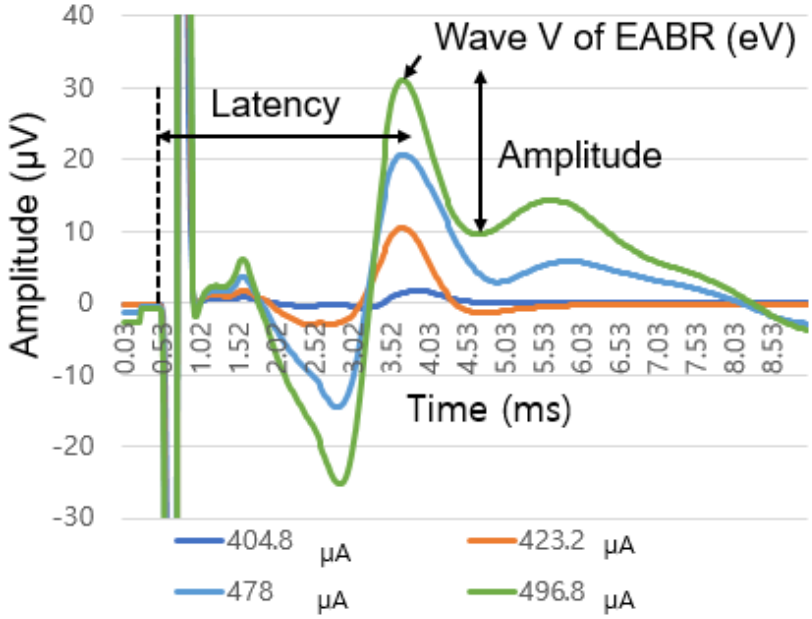
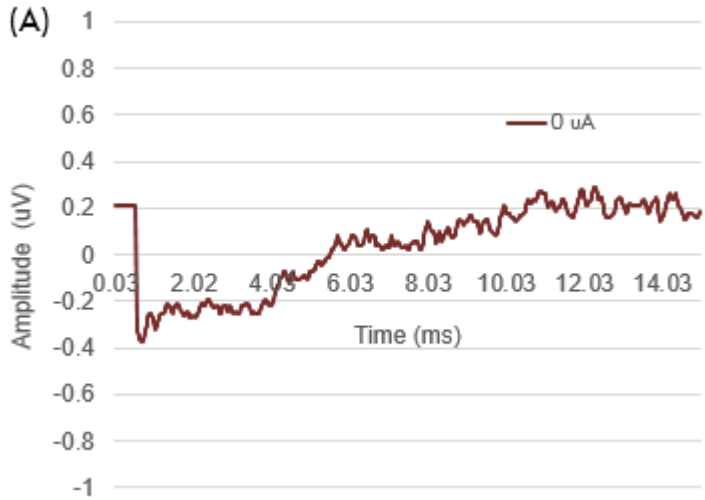


Figure 9. Measurements of EABR waveform. The latency and amplitude of eV were obtained for detailed analysis.



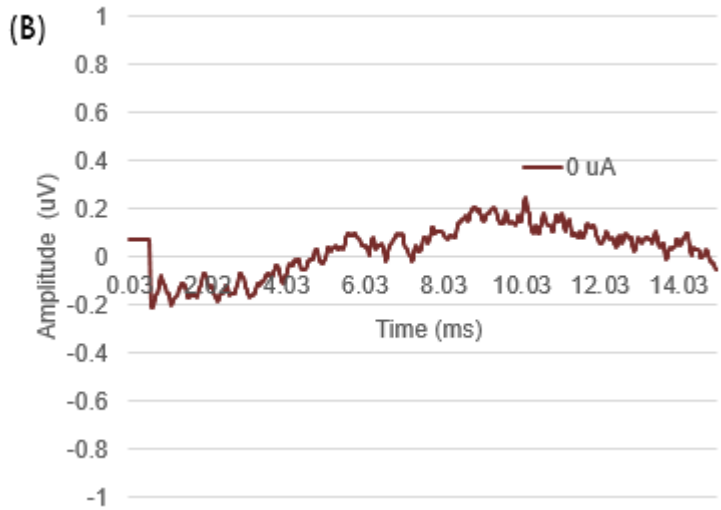


Figure 10. Representative figure of the noise floor of measured waveforms without electrical stimulation (subject no. NH01_L_210517). (A) and (B) were measured with Ch-A and Ch-B stimulation, respectively. Signal smaller than noise floor was not included for data analysis.

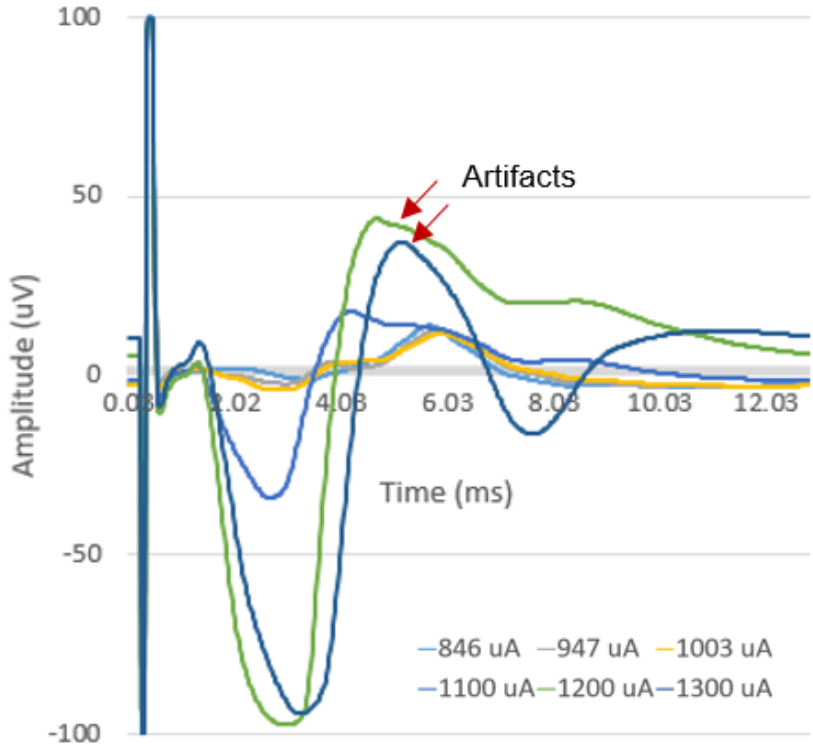


Figure 11. Artifacts produced by facial nerve or myogenic response (subject no. D4, Ch-B). The eV waveforms were recorded until it became difficult to observe due to the artifacts.

2.4. Histology

To measure the density of spiral ganglion neurons, animals

were sacrificed to cardiac perfusion using phosphate-buffered saline (PBS) and 4% paraformaldehyde under deep anesthesia. The cochlea was harvested from the five 8-week-old in normal hearing subjects and four subjects in the deaf group, fixed for 24 hours, and rinsed with PBS. Decalcification was done with 10% ethylenediaminetetraacetic acid (Santa Cruz Biotechnology, Santa Cruz, CA, USA) for four weeks. Then, embedded in paraffin, and 5 ㎛ sections were done every 200 um perpendicular to the axis of the modiolus of the cochlea. The sections were mounted on the glass slides and stained with hematoxylin & eosin. They were imaged with an uplight microscope (CX31, Olympus, Tokyo, Japan). The area of Rosenthal's canal and the number of type I spiral ganglion neurons within it were counted using ImageJ software (National Institutes of Health, Bethesda, MD, USA). The density of spiral ganglion neurons (neurons/mm^2) was calculated by dividing the number of spiral ganglion neurons by the area of Rosenthal's canal[57, 58].

2.5. Statistical Analysis

Two-tailed analyses were conducted for all parameters of EABR and density of spiral ganglion neurons using the Mann–Whitney U-

test. All data were shown as mean ± standard deviation, and all statistical analyses were performed using Prism software (Prism 5.0, Graph Pad, CA, USA). The statistical significance was set at $P < 0.05$.

Chapter 3. Results

3.1. Neural Stimulator and Electrode

3.1.1. Neural Stimulator

The developed neural stimulator can current balanced bi-phasic stimulation like electrical stimulation of a cochlear implant that stimulates the auditory nerve (Fig. 12). Development of Housing, firmware, and user interface program was done with the help of TODOC (TODOC CO., Ltd., Seoul, ROK). Efficient stimulation is possible with negative phase first stimulation, and current balancing between negative and positive phases has the advantage of minimizing cell damage.

Figure 12. Neural stimulator and user interface based on Android OS.

A load resistor was connected to both ends of one channel output of the developed neural stimulator. The stimulation waveform output was checked according to parameter adjustment and external trigger output to link to the evoked potential recorder (Fig. 13).

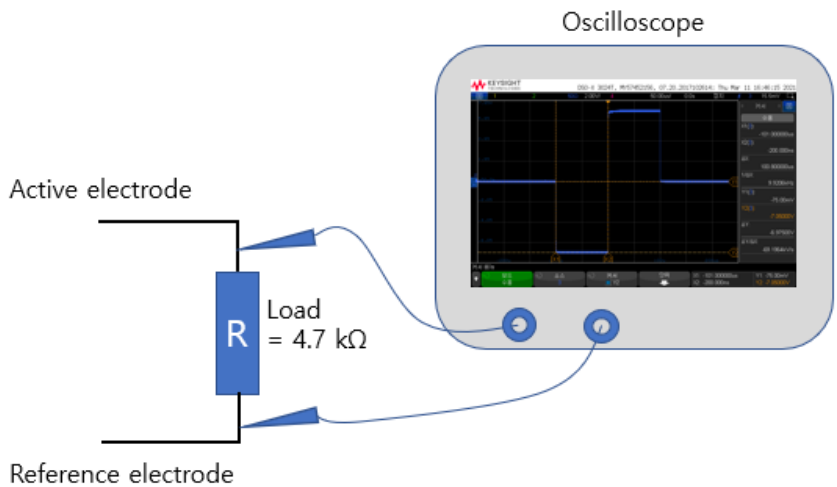


Figure 13. Block diagram of tests for verification of the promontory stimulator

Pulse amplitude, pulse width, and pulse rate were adjusted, and the output of the stimulation pulse was checked. The amplitude, width, and rate of stimulation pulses were adjusted as intended using the user interface for parameter configuration, and the measured value showed an error rate of less than 6% compared to the true value (Table. 2-5).

Table 2. Verification of function of pulse amplitude modulation (Channel 1, pulse width 100 ㎲/ph, pulse rate 30 Hz, load 4.6 kΩ (measured))

Pulse amplitude						
Current intensity (㎂)	True value (mV)		Measured value (mV)		Percentage error (%)	
	Negative phase	Positive phase	Negative phase	Positive phase	Negative phase	Positive phase
0	0	0	0	0	0	0
10	-46.01	46.01	-43.75	43.75	4.91	4.91
100	-460.10	460.10	-462.50	435.00	0.52	5.46
200	-920.20	920.20	-906.25	900.00	1.52	2.20
500	-2300.50	2300.50	-2275.00	2187.50	1.11	4.91
1000	-4601.00	4601.00	-4550.00	4350.00	1.11	5.46
1500	-6901.50	6901.50	-6993.75	6881.25	1.34	0.29

Table 3. Verification of function of pulse duration modulation (Channel 1, pulse amplitude 1500 ㎂, pulse rate 20 Hz, load 4.6 kΩ (measured))

Pulse width					
True value (㎲)		Measured value (㎲)		Percentage error (%)	
Negative phase	Positive phase	Negative phase	Positive phase	Negative phase	Positive phase
50	50	50.4	50	0.8	0
100	100	100.8	100.2	0.8	0.2

Table 4. Verification of function of pulse rate modulation (Channel 1, pulse amplitude 1000 ㎂, pulse width 100 ㎲/ph, load 4.6 kΩ (measured))

Pulse rate		
True value (Hz)	Measured value (Hz)	Percentage error (%)
20.00	20.00	0.00
30.00	29.94	0.20
40.00	40.00	0.00
60.00	59.98	0.03

Table 5. Verification of output of external trigger pulse

Trigger pulse			
	True value	Measured value	Percentage error (%)
Pulse width (㎲)	270.00	272.00	0.74
Pulse amplitude (V)	5.00	4.93	1.40

3.1.2. Surface-Type Multichannel Electrode

A surface-type electrode of a size suitable for installation in a rat cochlea was designed. TODOC was manufactured based on the design. The stimulation electrode was four channels, 0.3 mm in diameter, 0.55 mm in spacing between electrodes, and the electrode impedance was 4.33 ± 1.09 kΩ (@ 1 kHz). There was one reference electrode separately, and the diameter was Φ 0.86 mm. The electrode substrate was patterned through laser machining after attaching a Pt-Ir film between liquid polymer crystal sheets and coated with silicone elastomer (Fig. 14) [45, 46].

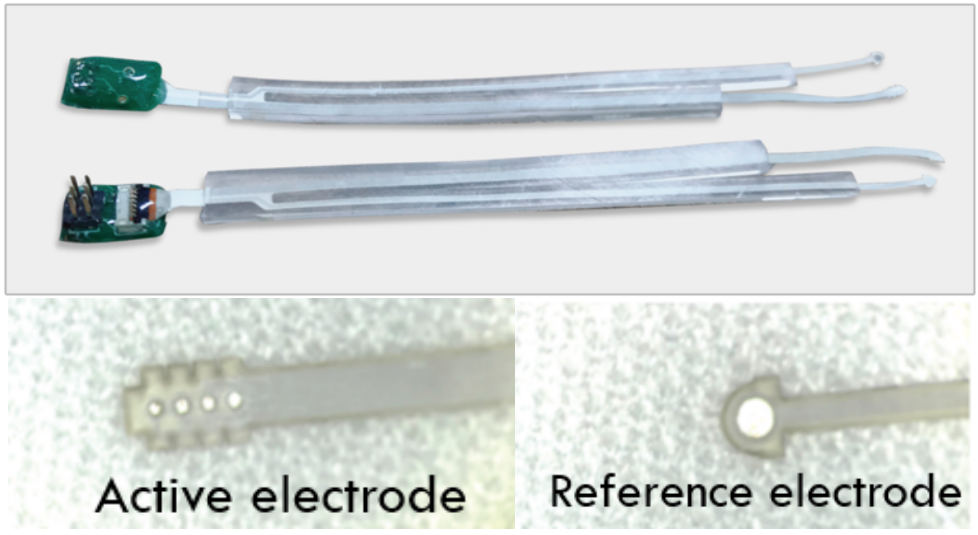
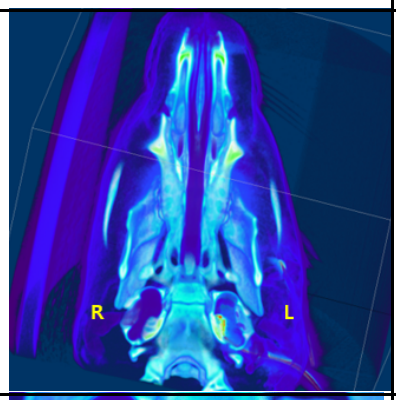
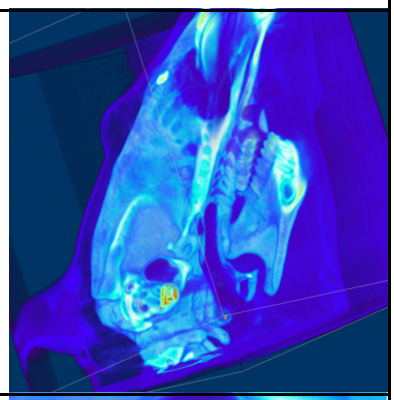
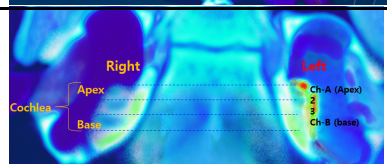
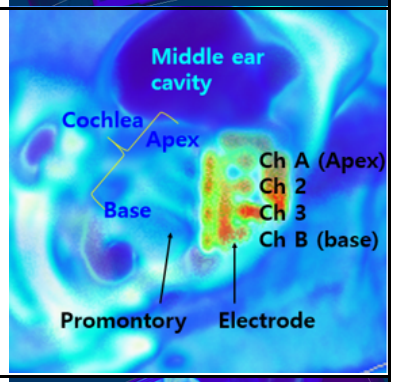
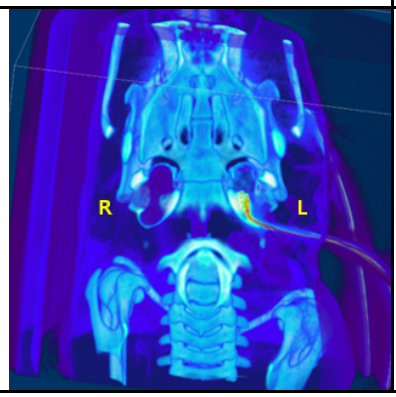
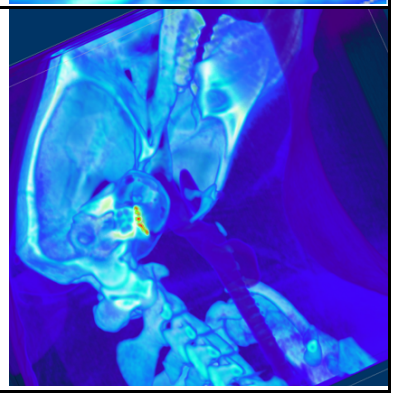


Figure 14. Produced four channel surface-type electrode. (Produced by TODOC (TODOC CO., Ltd., Seoul, ROK))

3.2. Electrode Position on the Promontory

To check whether the electrode installation was successful, microCT was taken, and 3D reconstruction was performed to observe the dorsoventral, ventrodorsal, and left lateral view (the dorsoventral and left lateral views were showed below). The electrode was placed on the promontory surface, and when the electrode was positioned correctly, channel A was located near the apex of the cochlea, and channel B was located near the base of the cochlea. An electrode was fixed in the normal hearing group on the left ear for three animals, and images were taken. Among them, the electrodes were positioned correctly on the cochlea in two rats, and the electrodes were not placed correctly in one rat. In one non-positioned animal, channel A was located outside the promontory, and channel B was located near the apex of the cochlea (Fig. 15). In the deaf group, microCT was performed on two animals, and one of the animals had the electrodes positioned correctly. In the remaining one, channels A and B were located in the apex and base of the cochlea, respectively, but were separated from the surface of the cochlea (Fig. 16).

Subject no.		Dorsoventral view	Left lateral view
NH5L	Zoom out		
	Zoom in		
NH6L	Zoom out		

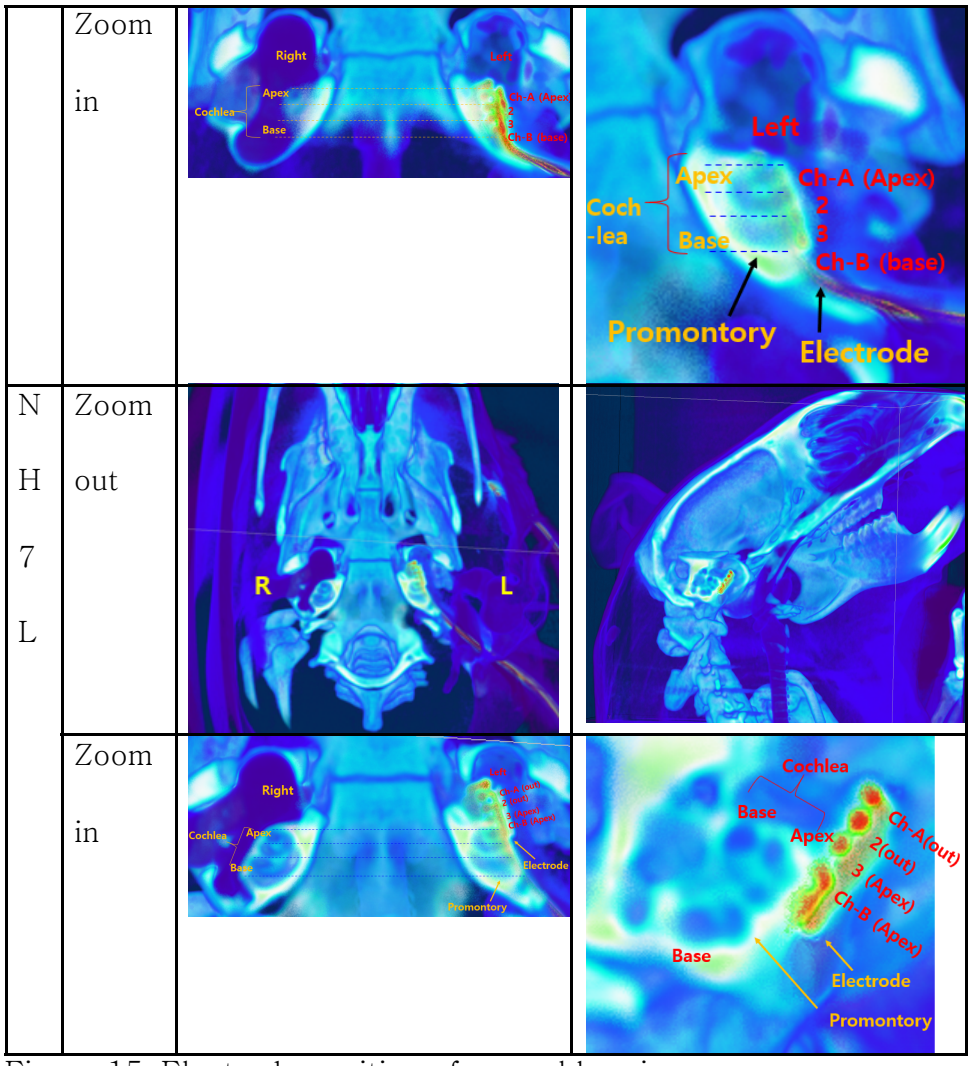


Figure 15. Electrode position of normal hearing group

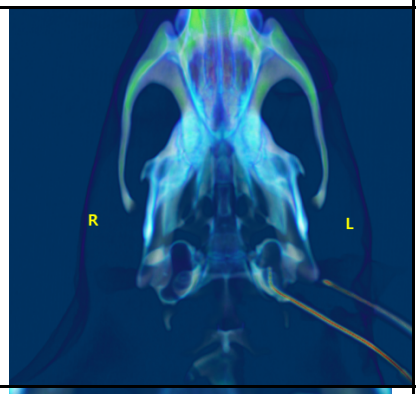
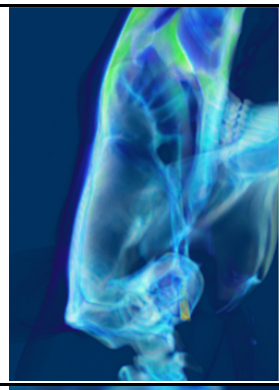
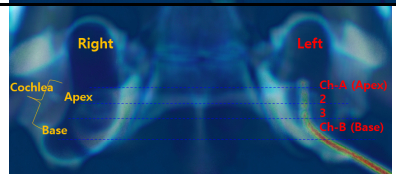
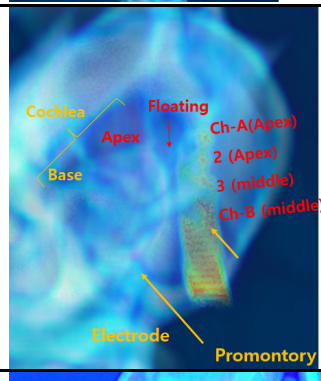
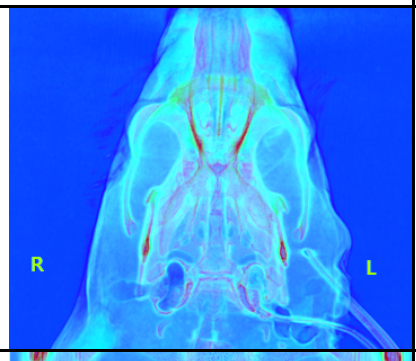
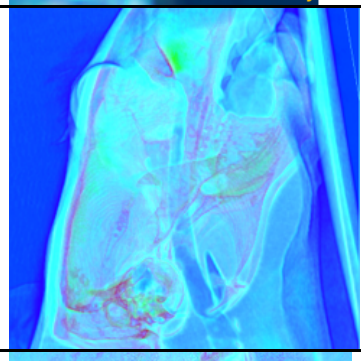
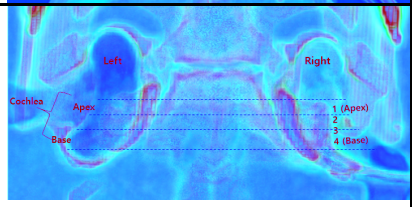
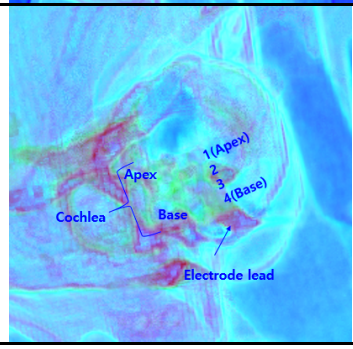
Subject no.		Dorsal view	Left lateral view
D 3	Zoom out		
	Zoom in		
D 4	Zoom out		
	Zoom in		

Figure 16. Electrode position of deaf group

3.3. Properties of EABR of Channel A and Channel B Stimulation

The x-axis of the amplitude growth function (AGF), and latency was expressed in the dB scale relative to the EABR threshold.

3.3.1. Comparison of Channel A and B in Normal Hearing Group

For AGF of the normal hearing group, the response to stimulation of the apical electrode was similar to or greater than that of the Ch-B stimulation in 3 out of 4 subjects. In the two subjects, the magnitude of the response increased rapidly as the stimulus intensity increased (Fig. 17). As a result of the statistical analysis of four animals, there was no significant difference between the two channels in AGF (Fig. 23). There was no statistically significant difference between the two channels. But the slope of AGF of all subjects of Ch-A is greater than Ch-B (Fig. 21). Latency of Ch-A was similar or longer than the Ch-B in some cases (Fig. 18), but Ch-A was significantly shorter (Fig. 25).

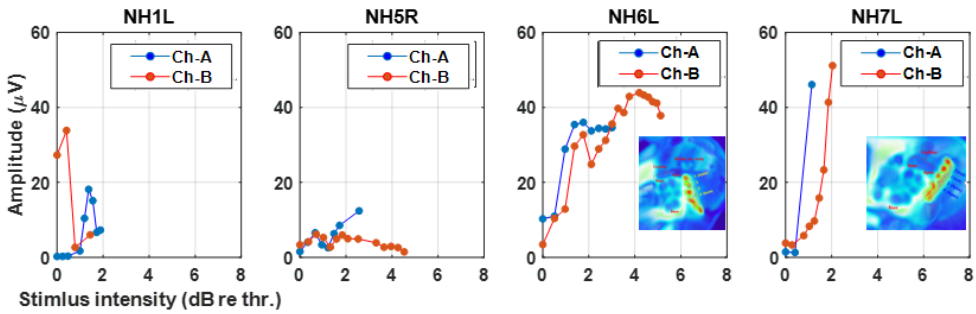


Figure 17. Channel difference of AGF in NH group. A CT image was inserted for the scanned subjects.

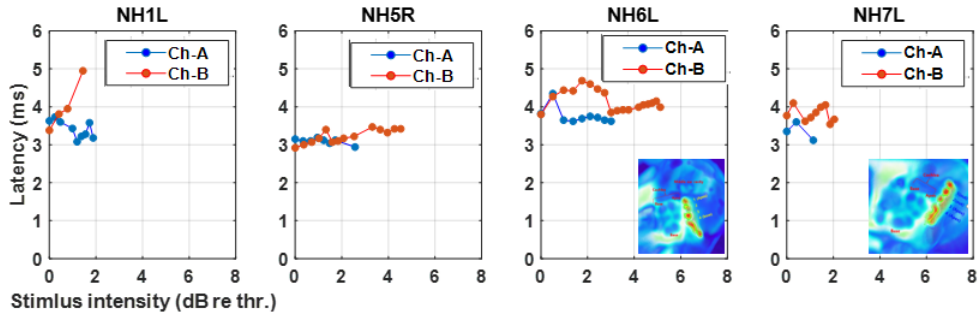


Figure 18. Channel difference of latency in NH group. A CT image was inserted for the scanned subjects.

3.3.2. Comparison of Channel A and B in Deaf Group

Two of them had a flat section in which the increase in response amplitude was not noticeable even when the stimulus intensity increased (D3 and D4). As the stimulus intensity continues to increase there was a stair section, where the reaction intensity increases stepwise in D4 subject (Fig. 19). However, there was no

significant difference between the two channels in AGF (Fig. 23). Latency was shorter in Ch-B than Ch-A in two rats but shorter in Ch-A in the remaining two rats (Fig. 20). As a result of statistical analysis, the latency of Ch-A was significantly shorter than that of Ch-B (Fig. 25).

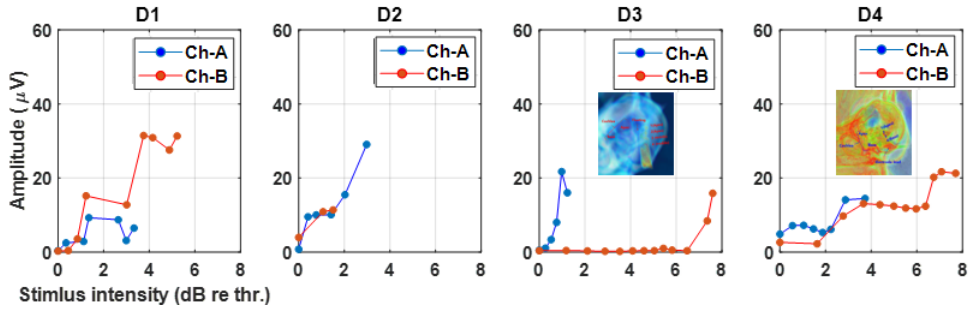


Figure 19. Channel difference of AGF in the deaf group. A CT image was inserted for the scanned subjects.

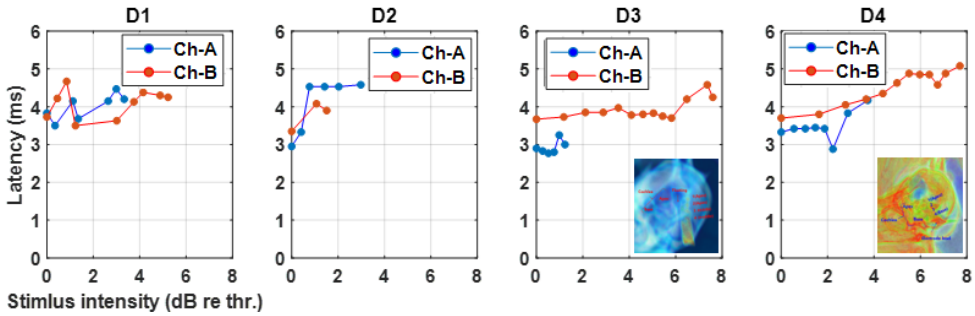


Figure 20. Channel difference of latency in the deaf group. A CT image was inserted for the scanned subjects.

3.4. Properties of EABR of Normal Hearing and Deaf

3.4.1. Comparison of AGF, Slope, Latency, and Threshold of in Normal Hearing and Deaf Group

In normal hearing group, amplitude of AGF was similar or greater in response to the stimulation of the Ch-A electrode compared to that of the Ch-B stimulation in 3 out of 4 subjects. Compared to the deaf group, the response amplitude increase was large even at a small stimulus intensity based on the threshold, and the response amplitude was saturated at a relatively low stimulus intensity. The linear trend lines of AGF using the data of all subjects in the normal hearing group showed a larger slope during Ch-A stimulation than during Ch-B stimulation (Fig. 21). The slope was 11.78 in Ch-A and 4.836 in Ch-B in the normal hearing group (Fig. 21). Latency was significantly shorter during Ch-A stimulation than in Ch-B stimulation. Latency had a negative slope during Ch-A stimulation and a positive slope during Ch-B stimulation (Fig. 21).

In the deaf group, the amplitude of AGF in one animal had a larger response upon Ch-B stimulation, but one animal showed a similar level, and two rats showed a slightly larger value upon Ch-A stimulation. Compared to NH, there were cases where the increase in response amplitude was small or maintained even when the

stimulus intensity increased. The slope of the linear trend line of the AGF using all individual data of the deaf group was smaller than that of the normal hearing group. The slope was 2.884 in Ch-A and 1.617 in Ch-B in the deaf group (Fig. 22). Latency was shorter in the case of Ch-B stimulation than in the case of Ch-A stimulation in one rat, but similar or shorter in the other three animals. The trend line of latency had a positive slope in both channels, and the slope at the peak stimulation was greater than the slope at the Ch-B stimulation (Fig. 22).

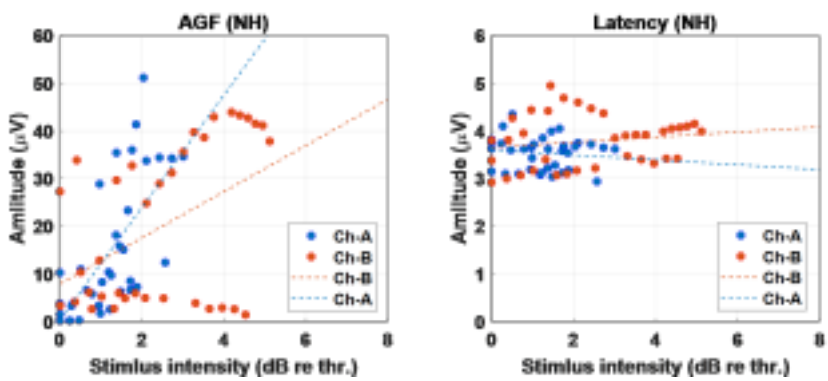


Figure 21. AGF and latency of all subjects in NH group. Blue and red dot lines are the linear trends of Ch-A and Ch-B, respectively.

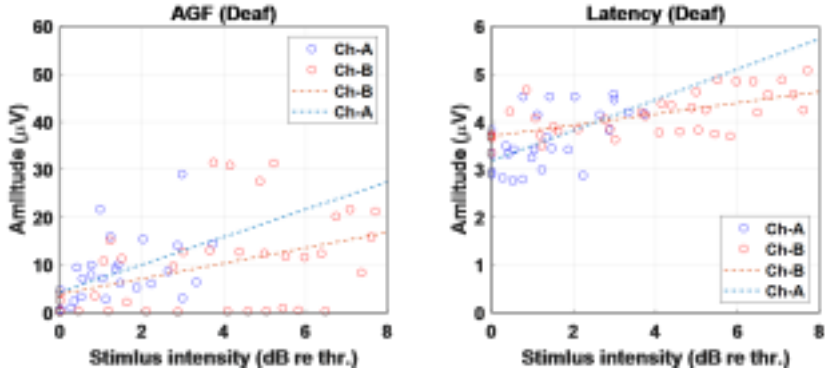


Figure 22. AGF and latency of all subjects in the deaf group. Blue and red dot lines are the linear trends of Ch-A and Ch-B, respectively.

3.4.2. Statistical Analysis of EABR Parameters of All Subjects in Normal Hearing and Deaf Group

For AGF, the normal hearing group Ch-B showed significantly higher values than the deaf group Ch-B and in other cases. There was a difference in the mean values, but it was not significant (Fig. 23). For EABR observed range of stimulus intensity, in the case of Ch-A stimulation, was shorter than Ch-B stimulation in both groups (Fig. 24). Ch-A showed shorter latency than Ch-B, regardless of hearing ability. And for Ch-B, the normal hearing group was shorter than the deaf group. Ch-A in the normal hearing group was

significantly shorter than Ch-B in the deaf group. (Fig. 25). Thresholds were higher at Ch-B stimulation in the normal hearing group and the Ch-A stimulation in the deaf group (Fig. 26). In the deaf group Ch-B was the lowest. These differences were not significant.

Table 6. Analyzed parameters (mean ± standard deviation)

Group	NH		Deaf	
Channel / Parameter	Ch-A	Ch-B	Ch-A	Ch-B
Amplitude (㎶)	15.04 ± 14.19	19.64 ± 16.58	8.31 ± 6.75	10.01 ± 9.90
EABR observed range (dB)	2.38 ± 0.52	3.69 ± 1.98	2.82 ± 1.10	5.51 ± 2.90
Latency (ms)	3.53 ± 0.35	3.78 ± 0.54	3.63 ± 0.61	4.14 ± 0.45
Threshold (㎂)	455.50 ± 120.78	542.30± 151.43	540.25 ±175.93	250.50 ± 151.99
SGN density (cells/mm^2)	1645.96 ± 373.39		583.86 ± 103.87	

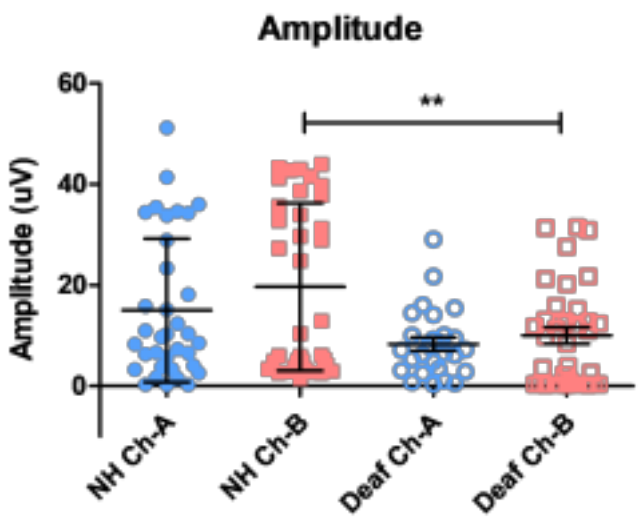


Figure 23. Comparison of amplitude of both groups and channels (*:

statistical analysis showed a significant difference)

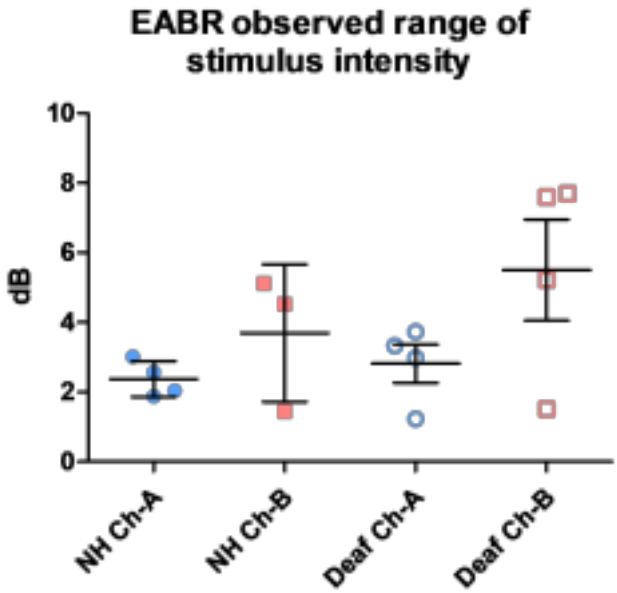


Figure 24. Comparison of EABR observed range of both groups and channels

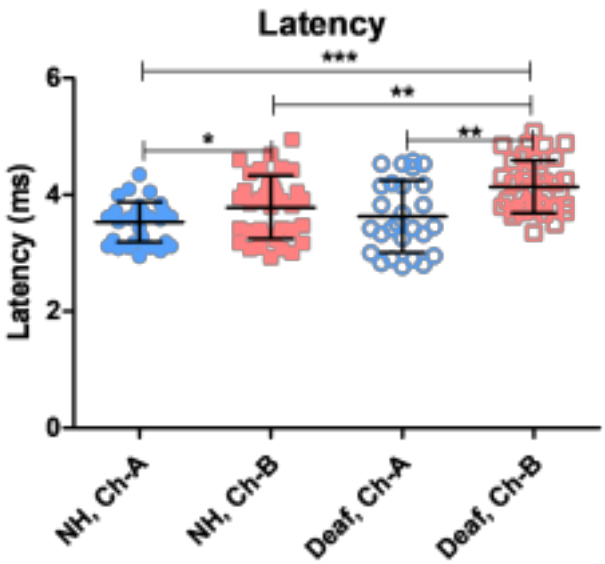


Figure 25. Comparison of latency of both groups and channels (*: statistical analysis showed a significant difference)

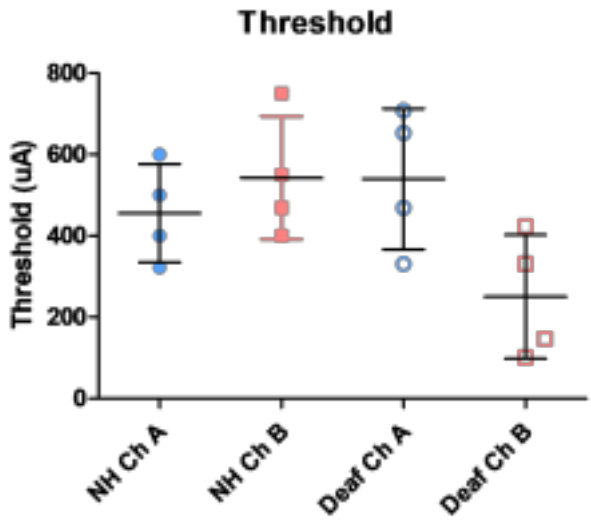
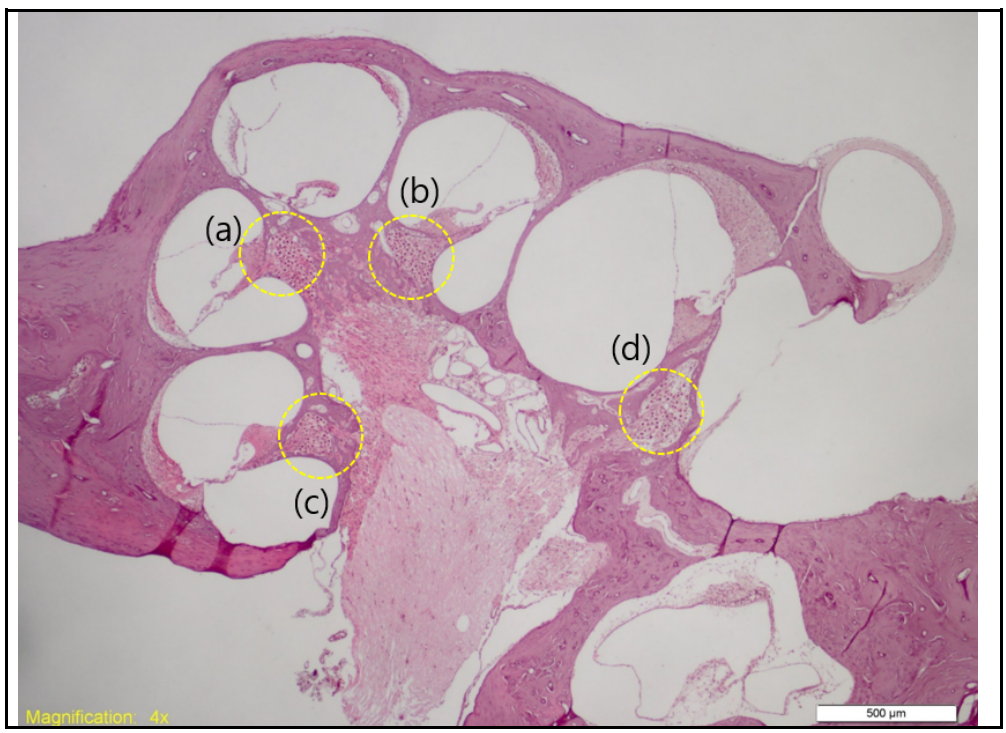


Figure 26. Comparison of threshold of both groups and channels

3.4.3. Density of Spiral Ganglion Neuron

Five cochleae from 5 animals with normal hearing (no EABR measurement) and four cochleae from 5 animals with hearing loss (4 animals in the deaf group were sacrificed after EABR measurement) were harvested and processed to get the cross-section image of the cochleae. The area of the Rosenthal's canals was measured, and the number of the SGNs was counted. Density was calculated as the number of SGNs divided by the area (Fig. 27, 28). The mean density of the normal hearing subjects was 1645.96 ± 373.39 neurons/mm2, and that of the deaf

subjects was 583.86 ± 103.87 neurons/mm2, and the difference between the two groups was statistically significant (Table 7, Fig. 23).



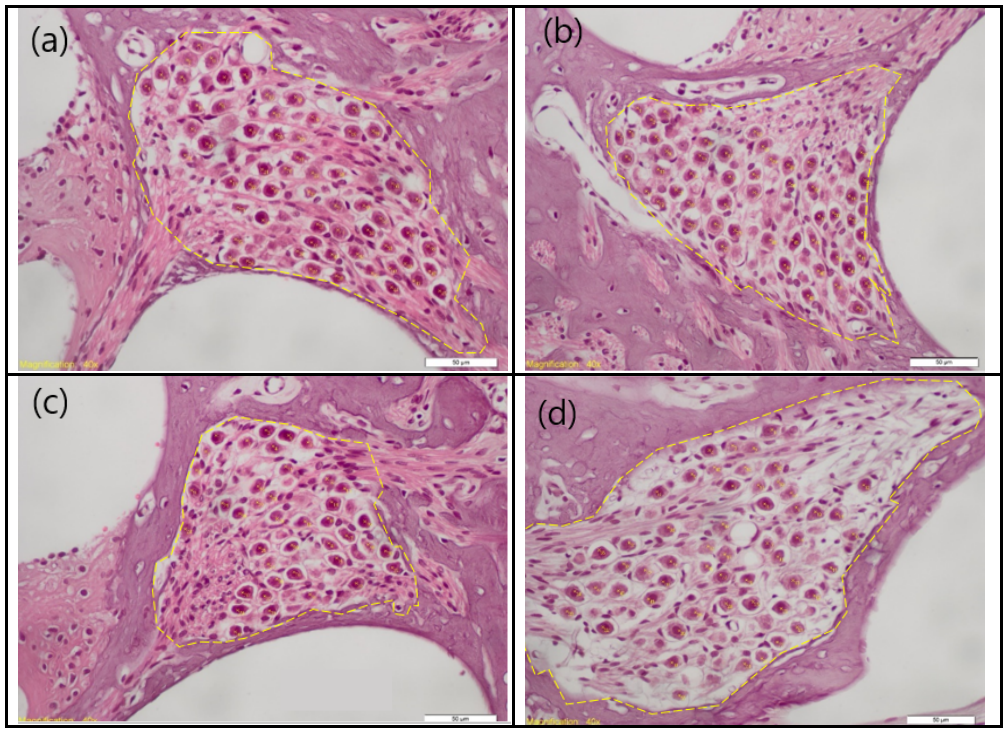


Figure 27. Representative image of a cochlea section in a normal hearing animal. Four Rosenthal's canals were used to get their area and the number of SGN

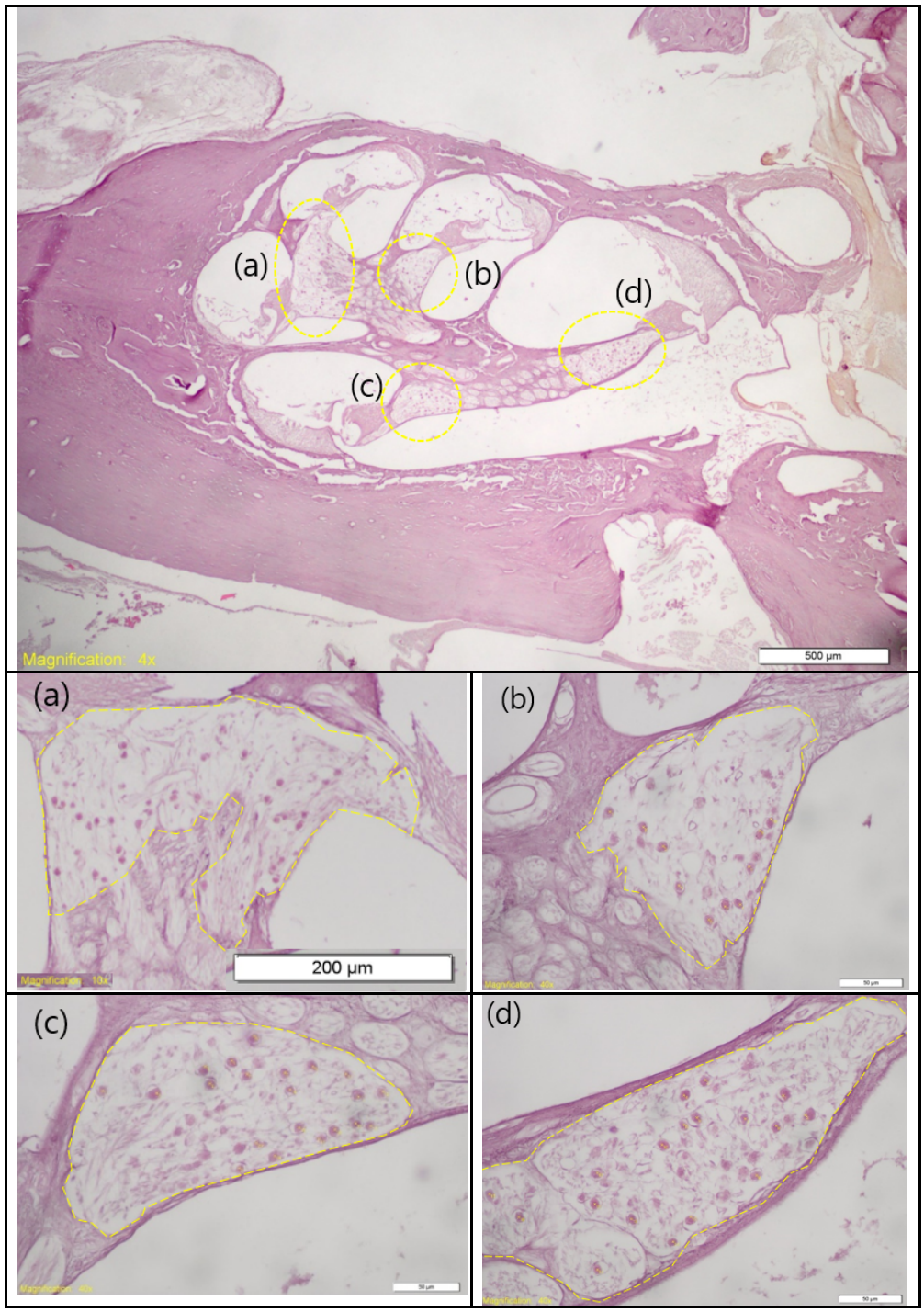


Figure 28. Representative image of a cochlea section in a deaf animal. Four Rosenthal's canals were used to get their area and the number of SGN

Table 7. Rosenthal's canal area, number of neurons, and density of SGNs per unit area in normal hearing and deaf animals

Normal hearing				Deaf			
No.	Area (mm^2)	Neurons	Density (Neurons /mm^2)	No.	Area (mm^2)	Neurons	Density (Neurons /mm^2)
N1	0.046	58	1260.87	D1	0.068	36	529.412
	0.03	55	1833.33	D2	0.088	51	579.545
N2	0.096	178	1854.14		0.105	70	666.67
	0.047	47	1000.00		0.068	32	470.59
	0.027	47	1740.74	D3	0.024	10	416.67
N3	0.033	61	1848.48		0.028	21	750.00
	0.022	52	2363.64		0.041	18	439.02
	0.026	41	1576.92		0.055	40	727.27
	0.05	48	960.00	D4	0.017	9	529.41
N4	0.062	122	1967.74		0.03	17	566.67
	0.023	41	1782.61		0.027	17	629.63
	0.026	43	1653.85		0.055	40	727.27
N5	0.027	44	1629.63		0.017	9	529.41
	0.028	44	1571.43	D5	0.03	17	566.67
					0.027	17	629.62963
Mean ± std	0.04 ± 0.02	62.93 ± 38.97	1645.96 ± 373.39	Mean ± std	0.05 ± 0.03	26.93 ± 17.57	583.86 ± 103.87

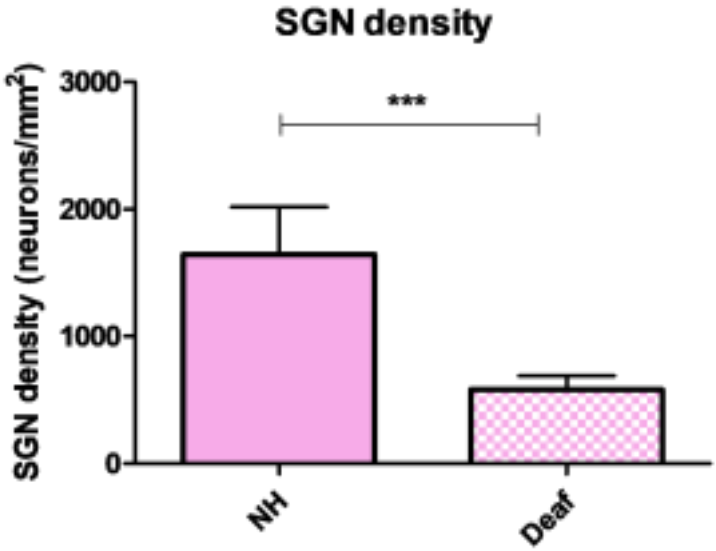


Figure 29. SGN density of NH and deaf group (*: statistical analysis showed a significant difference)

Chapter 4. Discussions

4.1. Comparison of Properties of EABR Between Channel A and Channel B

The neural stimulation device and surface-type electrode suitable for electrical stimulation of the animal cochlea were developed, and after fixing the electrode without trauma, EABR was successfully measured. In one subject, it was showed that the characteristics such as AGF, slope, and latency of the EABR obtained by electrical stimulation using two channels were different. The slope of the linear trend line for each stimulation channel of AGF and Slope was greater in the case of stimulation of Ch-A than that of stimulation of Ch-B. However, in the deaf group, the linear trend line of the slope was similar when both channels were stimulated. In the case of latency, both the normal hearing group and the deaf group were shorter during Ch-A stimulation. EABR was observed over a wider range of stimulus intensity during Ch-B stimulation, regardless of the presence or absence of EABR according to stimulus intensity. This is similar to the results of

other studies that showed greater and faster response intensity and steeper AGF slope upon stimulation of the apical cochlea.[28, 29, 59]. In other studies, it was expected that by changing the cochlear implant stimulation mode or parameters, it would be helpful to improve the spectral resolution or reduce noise by controlling the current spread of excitation. [34, 35].

4.2. Comparison of Properties of EABR between Normal Hearing and Deaf

Compared to the deaf group, the normal hearing group showed a larger AGF and slope, and shorter latency. This means that the range of current-stimulated auditory nerve cells may vary depending on the physical location of the electrode. It is believed that the difference in the analyzed parameters reflects the characteristics according to the number and distribution of stimulated spiral ganglion cells. In another study examining the characteristics of AGF in subjects with normal hearing compared to subjects with hearing loss, it is known that AGF exhibits a steeper slope and greater response amplitude [28, 29, 59]. In the AGF of the

deaf group, there is a section where the EABR response intensity does not increase even when the stimulus intensity increases (flat section). However, if the stimulus intensity continues to increase, there is a part where the reaction intensity increases stepwise (stair section). This section is related to the number or distribution of SGNs included in the stimulus. When the degeneration of SGN is stimulated, a flat section appears. As the stimulation intensity continues to increase and the range of electrical stimulation expands, newly recruited SGNs affect the EABR response. It is believed that contributing may show the stair section. In another study, the deaf group was known to have a smaller and shallower AGF than the normal hearing group, but the SGN model was not degraded for each cochlea turn [28, 29]. However, it was shown that the SGN density had a positive correlation with the AGF slope, suggesting that the AGF slope may be small or flat in the area with little or no SGNs.

As for the latency trend line, Ch-A of the normal hearing group had a negative slope, but the rest had a positive value. The Ch-B stimulation of the normal hearing group was significantly shorter than the Ch-B stimulation of the deaf group, and the Ch-A stimulation of the normal hearing group was significantly shorter than the Ch-B stimulation of the deaf group, showing the largest

difference. This is partially consistent with other studies showing that EABR latency is significantly shorter in animals with normal hearing or hearing recovered [60, 61].

There was no significant difference in threshold between the groups, and the SGN density showed about 2.9 times more cell density in the normal hearing group than in the deaf group. If the condition of the electrode-tissue interface is the same, the threshold of normal hearing subjects with high SGN density is lower than that of hearing loss subjects [60]. In this study, it could not be confirmed due to the absence of the impedance measurement function of the electrode connected to the neurostimulation device, and the number of experimental subjects was also small, suggesting that there was no difference between groups.

4.3. Clinical Implications

As shown in the results of this study, EABR induced by stimulation of the cochlea using multichannel electrodes before, during, and after cochlear implant surgery in clinical practice was measured, and it may be more accurate than the past promontory stimulation test using single-channel electrodes.

If a multichannel electrode that can be applied to the promontory and applied to the promontory through the external auditory canal of the human ear for stable electrical stimulation is fabricated, simple local anesthesia is performed on an outpatient before cochlear implant surgery in the clinic, and then the eardrum is incised to stimulate the promontory multisite for measuring response of auditory periphery. This test result can serve as a basis for deciding whether to undergo cochlear implant surgery as a preoperative auditory function evaluation [3, 62].

After exposing the patient's promontory in the operating room, multichannel electrodes can be used to stimulate multiple positions, and the characteristics of EABR can be examined, which can be used as a basis for a decision on cochlear implant surgery [19, 63]. If the results of cochlear implant rehabilitation are not expected through auditory function evaluation, avoid opening the implant package to reduce unnecessary costs, be careful not to be exposed to an environment with high electromagnetic fields after cochlear implant surgery. It is possible to avoid disadvantages such as not being able to see the tissue state near the implant due to image distortion [64].

If necessary, even after cochlear implant surgery, the auditory function can be evaluated using multichannel electrodes that can be

applied to the promontory through the eardrum as in the method before surgery above. Although the implant operates normally and the stimulus parameters are adjusted to suit the user, even if the benefit of hearing recovery is reduced or absent, this auditory function evaluation method is used to estimate the response of the auditory nerve, the number or distribution of ganglion cells and take the necessary action.

4.4. Limitation of This Work and Future Direction

4.4.1. Design and type of electrode, Electrode Installation, and Fixation

A multichannel surface-type electrode suitable for electrical stimulation of the cochlea of animals was developed. Electrodes were fixed on the promontory surface, and microCT scans of 5 animals were performed to confirm the electrode positions. In two of these, electrodes were found to be unintentionally pushed out or displaced from the cochlear surface. It was confirmed that Ch-A of individual number NH7 of the normal hearing group was out of the

promontory, and Ch-B was located on the cochlea apex side and protruded distal with respect to the cochlea modiolus axis. In subject D3 of the deaf group, the electrode was not in close contact with the promontory, but the electrode and the promontory were wet with body fluid, so electrical stimulation stimulated the promontory, and EABR was observed. It is necessary to improve the electrode design and fixation method so that the electrode is positioned on the promontory as intended and does not move after fixation. It is also necessary to compare it with the needle electrode used in existing clinical studies [65]. Suppose there is no superiority between the electrode types. In that case, the needle electrode can stimulate several places on the promontory surface like a multichannel electrode by developing a method for determining stimulation location, securing space for electrode movement, and developing a stable fixation method.

4.4.2. Condition of Electrode-Tissue Interface

The surface-type multichannel electrode was developed in an appropriate form considering the shape and the size of the animal's promontory. But, after installing the electrode, a microCT scan of

some subjects confirmed that the electrode was out of position. The neurostimulator developed for this study has no electrode impedance measurement function. By developing this function to check the state of the electrode-tissue interface, it will be possible to know whether the electrode is well installed on the promontory [66]. And it will be possible to assure the reliability of the electrical stimulation applied through the electrode.

4.4.3. EABR Study using Partial Hearing Loss Model

In the AGF of the deaf group, there was a flat section, where the EABR response intensity does not increase as the stimulus intensity increases. And there was a stair section, where the reaction intensity increases stepwise as the stimulus intensity continues to increase. The cochlea is composed of apex, middle, and base. The apex is low-frequency specific, and the base is high-frequency specific. These sections are related to the population or distribution of SGNs [67, 68]. So, it is considered necessary to study the EABR characteristics after inducing SGN degeneration for each cochlea turn using the partial hearing loss model. Therefore, it is possible to estimate of the population or distribution of SGNs

through EABR observation according to stimulation for each part of the cochlea using partial hearing loss model.

Chapter 5. Conclusion

5.1. Summary and Clinical Implications

After installing and fixing multichannel electrodes on the promontory in normal hearing and deaf groups, the wave V characteristics of EABR were observed by promontory electrical stimulation. The AGF, slope, latency, and threshold of the EABR according to the electrical stimulation strength were analyzed.

The amplitude and slope of AGF were larger in Ch-A stimulation than in Ch-B stimulation in normal hearing and deaf groups. Latency was shorter during Ch-A stimulation in both groups. Compared to the deaf group, the normal hearing group showed a larger slope of AGF, and shorter latency. It was shown that there is a difference in the EABR characteristics according to the stimulation channel, that is, the cochlea stimulation site and the difference between the normal hearing and deafness animal groups was also confirmed. Promontory stimulation using multichannel electrodes could be used to estimate SGN distribution by measuring the flat and stair section

of AGF of EABR. The results of this study are expected to be used for the perioperative evaluation of auditory function like diagnostic tests for cochlear implant candidates, prediction of rehabilitation outcomes after cochlear implantation, and improvement of the stimulation strategy of the cochlear implant.

5.2. Limitations of This Study and Further Study

When the electrodes are in position, Ch-A is located on the apical side of the cochlea, and Ch-B is located on the basal side of the cochlea. The installed electrodes were dislocated in two out of five animals based on the microCT image. In the future, it is necessary to improve the electrode design, installation, and fixation method for the evaluation of auditory function by promontory stimulation. Furthermore, it is required to study the evoked response using multichannel surface-type or other type electrodes in the partial hearing loss model with SGN degeneration of a specific cochlea turn.

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Abstract

Promontory Electrically Evoked Auditory Brainstem Response for Perioperative Evaluation of Auditory Function in Cochlear Implant

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서론: 인공와우는 보청기를 이용하여도 소리를 들을 수 없는 중고도 감각신경성 난청인을 위한 청각재활장치이다. 이 장치는 난청인의 달팽이관에 전극을 이식되어 소리정보가 담긴 전기자극으로 청각세포를 직접 자극하여 청력을 회복시켜준다. 인공와우 수술 후 예후예측을 위하여, 수술하기 전에 난청인의 청각계의 상태를 확인하는 것은 매우 중요하다. 전기자극 유발반응 관찰은 기존연구들을 통하여 유용성이 알려졌지만, 신뢰성 부족, 자극위치 확인 어려움, 단채널 전극으로 인한 제한적인 자극범위 등으로 임상적으로 거의 쓰이지 않고 있다. 본 연구에서는 와우갑각의 자극 위치변경에 따른 청신경 자극 유발 전위의 특성에 변화가 있는지 관찰하여, 와우갑각의 다채널 자극을 통한 청각기능평가의 필요

성을 확인하였다.

방법: 동물의 와우갑각에 배치, 고정하기에 적합한 형태의 표면형 다채널 전극을 제작하고, 전기자극이 출력되는 신경자극장치를 개발하였다. 정상 청력 4마리, 난청 동물 4마리에 대하여 달팽이관의 뼈 벽인 와우갑각에 다채널 전극을 설치하여 달팽이관의 apex에 가까운 곳에 Ch-A, base에 가까운 곳에 Ch-B가 위치되도록 한다. 정상청력개체 3마리, 난청개체 2마리에 대하여 전극위치 확인을 위해 microCT촬영을 하였다. 두 개 채널을 이용하여 청신경을 전기자극하여 유발되는 전위 electrically evoked auditory brainstem response(EABR)를 측정하고, wave V의 amplitude growth function(AGF), slope, latency 등을 분석하였다. 정상청력, 난청, Ch-A자극시, Ch-B자극시의 4개 조합에 대하여 통계분석을 시행하였다. 정상청력, 난청동물의 달팽이관의 조직병리를 통하여 전기자극되어 청각계 활성에 기여하는 spiral ganglion neuron의 밀도 또한 비교하였다.

결과: 전극설치 후 microCT 촬영결과, 정상청력군 2마리는 전극이 와우갑각에 정위치하였고, 1마리는 정위치 하지 못하였다. 난청군은 1마리는 정위치하였고, 1마리는 와우갑각 표면에서 이격되어 있었다. AGF는 전극위치가 확인된 개체에서 청력에 상관없이 Ch-A가 Ch-B에 비하여 amplitude가 더 크고 기울기가 급한 구간이 많았다. Amplitude는 Ch-B에서 NH군이 deaf군에 비해 유의미하게 컸다. 각 군의 모든 개체에 대한 slope는 청력에 관계없이 Ch-A에서 Ch-B에 비하여 컸다. 정상청력군의 Ch-B가 난청군의 Ch-A에 비해 유의미하게 컸다. EABR이 관찰된

stimulus intensity의 범위는 Ch-A보다 Ch-B 자극의 경우 더 넓었다. Latency는 청력에 관계없이 Ch-A자극한 경우가 Ch-B자극한 경우에 비하여 유의미하게 짧았다. Ch-B에 대하여는 정상청력군이 난청군에 비하여 짧았고, 정상청력군의 Ch-A자극한 경우 난청군 Ch-B자극한 경우에 비하여 유의미하게 짧았다. Threshold는 유의미한 차이는 없었고, 단위면적당 spiral ganglion neuron의 밀도는 정상청력군이 난청군보다 약 2.9배 높았다.

결론: 동물 와우갑각 전기자극에 적합한 신경자극장치와 표면형 다채널 전극을 개발하고 와우갑각에 전극을 고정한 후 EABR을 성공적으로 측정하였다. 와우갑각의 서로 다른 위치를 자극하기 위하여 두 채널을 자극하여 획득한 EABR의 AGF, slope 등의 특성에 차이가 있음을 확인하였다. 전극의 물리적 위치에 따라 전류자극되는 범위, 자극되는 나선신경절 세포의 개수와 분포에 따른 특성이 반영되었기 때문일 것으로 여겨지며, 임상에서 청각기능 평가를 위하여 promontory stimulation을 할 경우에는 다채널 전극을 이용한 평가의 필요성이 요구된다고 사료된다. 그러나 전극이 의도되지 않은 위치에 고정된 경우가 있어 추후 연구를 위하여는 전극배치와 고정방법의 개선 및 전극설치 후 electrode-tissue interface 상태 모니터 기능이 필요하다. 또한 partial hearing loss model에 대하여 와우갑각의 다양한 위치를 자극한 청신경 반응 특성의 관찰이 필요하다. 이를 통하여 인공와우 대상자에 대하여 수술기주위에 청신경 상태를 객관적으로 진단하고, 청각재활 결과의 예후 예측에 활용을 기대할 수 있을 것이다.

핵심단어: 인공와우, 청각기능평가, 와우갑각자극, 다채널 전극, 전기유발 청성뇌간반응, 수술기주위, 예후예측

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