Table 1 – Time constant (TC) of horizontal (H) and vertical (V) components (s)

Head position		H-comp. TC (s)	V-comp. TC (s)
Initial 30°	Tilt toward UP (30° → 0°)	4.8 ± 3.3	1.5 ± 0.7*
	Tilt toward SD (30° → 60°)	3.1 ± 1.8**	6.1 ± 3.8
	No-tilt (30°)	5.1 ± 2.9	5.6 ± 2.9
Initial 45°	Tilt toward UP (45° → 15°)	4.9 ± 2.4	2.4 ± 0.9**
	Tilt toward SD (45° → 75°)	3.7 ± 1.2**	8.3 ± 1.6
	No-tilt (45°)	6.5 ± 1.0	7.1 ± 1.4
Initial 60°	Tilt toward UP (60° → 30°)	4.0 ± 2.7	3.0 ± 1.8**
	Tilt toward SD (60° → 90°)	2.2 ± 0.6**	7.8 ± 2.1
	No-tilt (60°)	5.0 ± 1.8	6.7 ± 2.4

Statistically significant: *$P < 0.05$, **$P < 0.01$, re No-post-rotatory-tilt. Head position "90°" corresponds to side down (SD) and "0" corresponds to upright (UP). $N = 4$.

always work simultaneously. For head-pitch tilt, there is little reorientation with shortened TC (humans: (Fetter et al., 1992, 1996); cats: (Yasuda et al., 2003)). In general, when humans and cats are in motion they are usually walking on the ground; in daily life, they don't often have the side of their head on the ground. Monkeys, on the other hand, move more freely in space. For example, the rhesus monkey, which was used in a previous study (Angelaki and Hess, 1994a), is both arboreal and terrestrial. Reorientation, which may act as an inertial navigation system via its gyroscopic ability, may be of advantage to the perception of spatial verticality, especially when the head and body are not upright in arboreal life. In cats and humans, as opposed to monkeys, the maintenance of balance and orientation in space during locomotion may not depend much on reorientation. The canceling of PRN may be important when the head is tilted away from the upright position, since the subject is not in fact rotating. The differences between species may reflect specific adaptations to the expected relationships between head movements and changes in orientation with respect to gravity.

The average TC without head tilt in the present study was similar to that reported by Harris LR (Harris, 1987), but was rather short compared to that of previous literature reports (Harris and Cynader, 1981; Robinson, 1976). This difference may be due to repeated exposure to rotation, albeit over an extended period, which is known to reduce the TC (Clément et al., 1981; Jäger and Henn, 1981).

Tilt-suppression as well as reorientation may be a central neuronal mechanism suitable for a gravitational environment. However, a human subject experiences a tumbling sensation of turning about a tilted axis and has postural instability during and after head tilt (Fitger and Brandt, 1982; Schrader et al., 1985a,b). At least for cats and humans, the central interactions between the semicircular canal and otolith inputs might be vestigial. Our data add to evidence that what is termed "tilt-suppression" depends on a change in head orientation with respect to the EVA.

4. Experimental procedures

4.1. *Animal preparation*

Four adult cats, weighing 2.0–3.0 kg, were used in this study. All were the same cats used in a series of our previous studies (Fushiki et al., 2004; Yasuda et al., 2002, 2003). The methods of surgical procedures and eye movement recording were also the same (Fushiki et al., 2004; Yasuda et al., 2002, 2003). In short, stainless steel head-restraining screws were implanted under pentobarbital sodium anesthesia (Nembutal, 35 mg/kg, ip). One week later, a scleral search coil was implanted in the frontal plane of the eye beneath the conjunctiva and around the cornea under pentobarbital sodium anesthesia and local anesthetic eye drops. The animals were given 2 weeks to recover from the surgery before being exposed to vestibular stimulation. All surgical and experimental procedures were approved by the Animal Experiment Committee of the University of Toyama of Japan, and were performed in accordance with the University of Toyama guidelines for the use of animals in experiments.

4.2. *Vestibular stimulation*

The cat's body was gently wrapped in a cloth bag. The head was fixed by the implanted head screws to a restraining bar attached to a stereotaxic frame, which was mounted on the inner table of a three-axis turntable (Daiichi Medical Co. Ltd., FAV-100S, Japan). The head and body of the cat were maintained at a roll angle of 45° with respect to earth vertical with the right ear down. The animals were rotated about the EVA to the animal's oblique right and up in total darkness at a constant velocity of 100°/s for 180 s with an acceleration and deceleration of 120°/s^2. Within 2 s after stopping EVA rotation, the animals were roll-tilted by 30° toward either the upright or the side down, or were maintained at a roll angle of 45°. The PRN was also induced with the animal's head/body maintained at a roll angle of 30 or 60°. The animals were roll-tilted by 30° from initial head-roll positions toward the upright or the side down. If a cat showed signs of discomfort, it was immediately released. No cat was ever sick or showed any signs of nausea.

4.3. *Eye movement recording and data analysis*

Eye movements were measured using a magnetic search coil system (Enzanshi Co. Ltd., MEL-45, Japan). The magnetic fields were mounted on the inner table of a computer-controlled vestibular turntable. Eye position and table position were then sampled at 100 Hz with a CED 1401-plus AD converter with the CED Spike2 program (Cambridge Electronic Design Ltd., Cambridge, UK) run on a PC. The eye movements were calibrated before each session by submitting the animal to sinusoidal rotations at 0.25 Hz ± 20° directly in front of a stationary random-dot pattern, under the assumption that compensatory eye movement gain was 1.0 during this condition (Keller and Precht, 1979; Maioli et al., 1983). The magnetic field coils were fixed relative to the animal. The direction of eye movement was specified with respect to the animal: Horizontal eye

movements are always from the animal's left to right, even if it is lying on its side. "Up" and "right" are indicated by positive voltages. Data analysis was performed with user-written programs. The fast phases of PRN were removed to obtain slow-phase eye velocity (SPV) records. The time-constant (TC) values for the horizontal and vertical components were determined by fitting the SPV records with a first-order exponential decay: $y = y0 + Ae^{-(x-x0)/t}$, where A is the amplitude and t is the TC. For PRN orientation, the horizontal (H) and vertical (V) components of SPV were vectorially combined at each time point to express an overall direction: angle of PRN plane = $\tan^{-1}$ (V-SPV/H-SPV). The final direction of the PRN plane after the head tilt was determined by fitting the angles of PRN with a straight line: $y = A + Bx$, where A is the intercept and B is the slope. The angle of the PRN plane represents the angle that the plane of eye movement makes with respect to the orbit. The angle "0°" corresponds to the orbital right, and the angle "90°" corresponds to the orbital up.

The average values for TC and angle of PRN plane were constructed for each cat and were then analyzed statistically. The statistical evaluations were performed using repeated measures ANOVA with post hoc Bonferroni correction. A difference was considered statistically significant at $P < 0.05$.

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ORIGINAL ARTICLE

Effects of selective cochlear toxicity and vestibular deafferentation on vestibular evoked myogenic potentials in guinea pigs

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Abstract

Conclusion: The findings suggest that sound-evoked myogenic potentials on the guinea pig sternocleidomastoid muscle (SM) originate from the vestibular end organ and not from the cochlea of the inner ear. *Objective:* Studies in animals of the sound evoked vestibular myogenic potentials on the SM should aid in elucidating the pathway of the vestibular-evoked myogenic potential (VEMP). However, details of the pathway of the VEMP remain to be elucidated. This study aimed to clarify aspects of this pathway. *Materials and methods:* In the present study, short latency biphasic myogenic potentials on the SM in guinea pigs were induced by an intense brief sound. *Results:* The thresholds of the potentials were 67 dB SPL above those of the auditory brainstem response (ABR). The potentials were eliminated by a vestibular deafferentation, but were observed after selective cochlea toxicity using an amikacin injection.

Keywords: *Sound-evoked potentials, sternocleidomastoid muscle, vestibular nerve section, amikacin, guinea pig*

Introduction

In humans, muscles of the neck and limbs contract in response to stimulation such as the sudden loud calling out of the individual's name. This is referred to as the startle reflex, and is a myogenic response originating from the cochlea. In addition, two kinds of myogenic potentials in response to loud acoustic stimulation are reported to originate from vestibular end organs, not from the cochlea. Bickford et al. [1] studied inion responses measured by electrode placement at the external occipital protuberance. These responses normally began 6–8 ms after stimulation and showed a four-phase wave within 50 ms. Colebatch et al. [2] recorded four- to five-phase myogenic potentials within 50 ms in response to loud clicks, using an electrode placed at the sternocleidomastoid muscle (SM). Both types of response have been recorded in subjects with profound deafness, but not in subjects who had undergone vestibular nerve section. The latter potential is referred to as the vestibular-evoked myogenic potential (VEMP) [3] and has been investigated as a clinical test for equilibrium function [4–7]. However, details of the pathway of the VEMP remain to be elucidated. Studies in animals of the sound evoked vestibular myogenic potentials on the SM should aid in elucidating the pathway of the VEMP.

To establish an animal model of the VEMP, we recorded myogenic potentials on the SM in response to brief intense sound in awake guinea pigs. The effects of the selective cochlear toxicity and vestibular deafferentation on these myogenic potentials were also investigated.

Materials and methods

Eighteen adult guinea pigs (400–600 g) with normal Preyer's reflexes were assigned to one of three groups. The control group consisted of 10 untreated guinea pigs (GP1–GP10). In the amikacin-treated group (four guinea pigs: GP11–GP14), amikacin sulfate (450 mg/kg) was injected intramuscularly for

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14 consecutive days to destroy the cochlea. In the vestibular deafferentation group (four guinea pigs: GP15–GP18), the vestibular nerve was sectioned. Myogenic potentials on the SM were recorded by electromyography (EMG), and results for the three groups were compared.

At least 7 days before recording, a pair of soft stainless-steel electrodes with a diameter of 0.08 mm (Unique Medical Co., Tokyo, Japan) was inserted into the left SM under anesthesia achieved by intramuscular injection of ketamine HCl (100 mg/kg) and xyladine HCl (4 mg/kg). The tips of the electrodes were positioned at the rostrocaudal half (active electrode) and at the sternal head (reference electrode) of the muscle (Figure 1A). The electrodes were connected to pins of a small integrated circuit (IC) socket, which was attached posterior to bregma with dental cement (UniFirst Corp., Tokyo, Japan). After surgery, cefotiam HCl (20 mg/kg; Takeda Inc., Tokyo, Japan) was administered intraperitoneally daily for 5 days to prevent infection. To record the auditory brainstem response (ABR), a pair of electrodes was placed at the bregma (reference electrode) and the midpoint between the external auditory meatus and bregma (active electrode). A small pore with a diameter of 1 mm was opened through the cranial bone with a dental drill, and a small screw was placed for the electrode to contact the dura mater. The ABR electrodes were also connected to the small IC socket.

For acoustic stimulation, a 4 kHz sine wave (0.125 ms) produced by an objective audiometry signal generator (Model DA-502A, Dana Japan, Tokyo, Japan) with a power amplifier (Model TA-N 330-ES, Sony, Tokyo, Japan) was used. Sound obtained by a receiver (ELEGA; Fujiki Electronics, Tokyo, Japan) was applied to the left external auditory canal via a silicon tube (external diameter 4 mm, internal diameter 2 mm, tube length 50 mm). To correct the sound pressure level, we used a 2 ml coupler with an attached sound level meter (Model NA-20, Rion Co. Ltd, Tokyo, Japan). The intervals of sound stimulation were 0.33 ms for the myogenic potentials and 0.1 ms for the ABR. During the

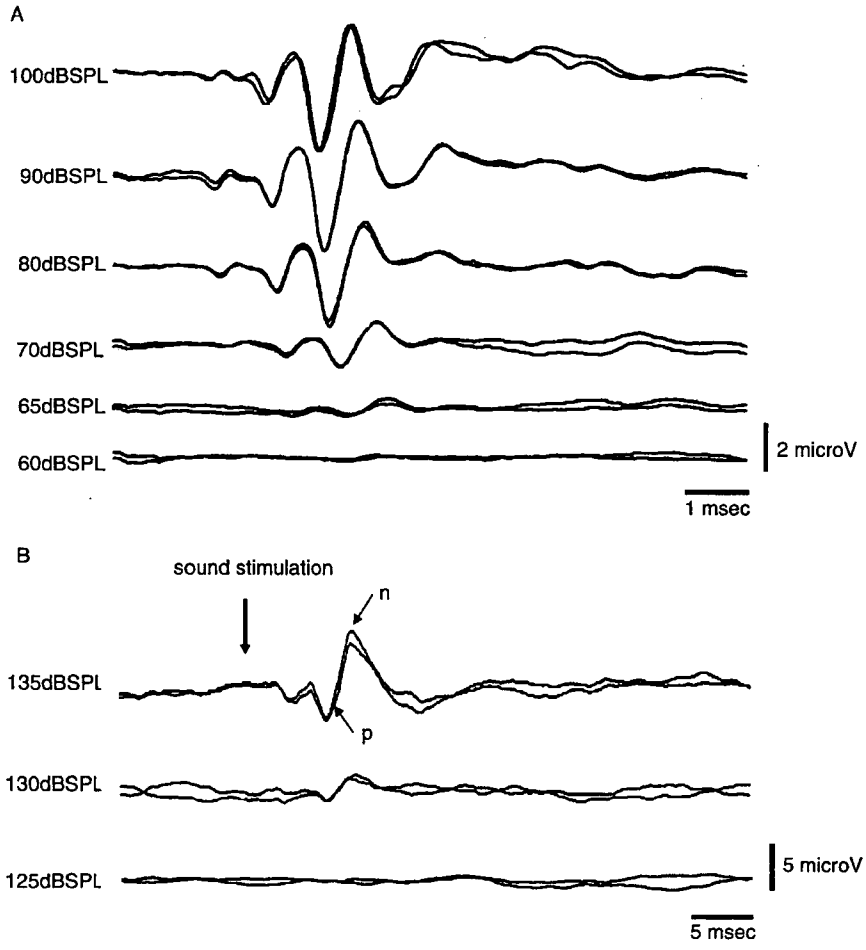

Figure 1. Waveform of the ABR and sound-evoked myogenic potentials on the SM to a brief intense sound in a normal guinea pig (GP1). (A) The threshold of the ABR was 65 dB SPL. (B) The threshold of the sound-evoked myogenic potentials was 130 dB SPL.

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experiments, guinea pigs were located in a sound-proof room and placed in a specially designed apparatus (Kurokawa Co., Toyama, Japan), consisting of rings for the neck and mouth that were large enough to allow the head and neck to move freely. Guinea pigs were placed in a prone position by adjusting the locations of the rings. A preamplifier (DPA-21E, Dia Medical, Tokyo, Japan) and a main amplifier (DPA-100EE, Dia Medical) and a MacLab 8S system (AD Instruments, Sydney, Australia) were used to analyze the data. Bandpath filters for EMG and ABR recordings were 5 Hz–2 kHz and 100 Hz–20 kHz, respectively. A total of 512 repetitions of the EMG recordings were averaged to determine the sound-evoked myogenic potentials on the SM, and a total of 1024 repetitions were used for the ABR. White noise of an intensity 30 dB SPL less than the stimulating sound was delivered to the contralateral ear in the vestibular deafferentation group.

Under anesthesia with intramuscularly injected ketamine HCl (100 mg/kg) and xyladine HCl (4 mg/kg), the subarcuate fossa was drilled out to expose the dura covering the cerebellar paraflocculus. After the dura was incised with a small needle, the paraflocculus was totally aspirated. The remaining empty dural sac was pushed dorsally and medially into the cranial cavity, which allowed for direct viewing of the vestibulocochlear nerve. The superior-posterior half of the nerve was transected carefully with a microknife. The ABR was recorded before and after sectioning of the nerve.

Administration of aminoglycosides is known to be ototoxic to the inner ear. It has been reported that administration of amikacin sulfate (450 mg/kg) for 14 consecutive days destroys most cochlear hair cells but not vestibular (saccule and utricle) hair cells in guinea pigs [8–11]. In this study, amikacin sulfate (450 mg/kg) injected into the gluteal muscle on 14 consecutive days was used to induce cochlear impairment.

The Wilcoxon rank-sum test was used for statistical analysis, which was conducted with StatView, version 4.1 software (Abacus Concepts Inc., Berkeley, CA, USA).

All procedures were performed in accordance with the principles of the Declaration of Helsinki and were approved by the Animal Ethics Committee of the University of Toyama.

Results

Control group

A representative ABR waveform from a normal guinea pig is shown in Figure 1A. The latency of each peak was prolonged when sound stimulation was decreased from 130 dB SPL to 70 dB SPL, and the response disappeared at 60 dB SPL. The mean threshold of the ABR from the 10 normal guinea pigs was 61.6 dB SPL (SD 7.1 dB SPL). A biphasic waveform was induced in response to an intense sound at the intensity of 135 dB SPL applied to the ipsilateral ear (Figure 1B). The latencies of the first positive wave (p) and the following negative wave (n) were 6.15 ms and 8.40 ms, respectively, and the peak-to-peak amplitude between the p and n waves was 11.9 μV. The onset latency of the p wave was 4.55 ms. The latency of the p wave was not delayed when sound intensity was reduced to 130 dB SPL. The threshold of the myogenic potentials was 130 dB SPL. The mean peak latency of the p and n waves from the 10 normal guinea pigs was 6.22 ms (SD 0.54 ms) and 7.73 ms (SD 1.14 ms), respectively, and the mean onset latency of the p wave was 4.85 ms (SD 0.82 ms). The threshold of myogenic potentials was 128.5 dB SPL (SD 6.3 dB SPL).

Amikacin-treated group

An ABR waveform similar to that observed in the control guinea pigs was observed in amikacin-treated guinea pigs (Figure 2A). However, the threshold of the ABR was 125 dB SPL. The mean threshold for the four amikacin-treated guinea pigs was 126.8 dB SPL (SD 9.7 dB SPL). The mean threshold of the ABR for the amikacin-treated group was increased compared with that in the control group ($p < 0.01$). Sound-evoked myogenic potentials on the SM were also recorded in this group (Figure 2B). At a sound stimulation of 135 dB SPL, the peak latencies of the p and n waves were 5.35 ms and 7.75 ms, respectively. The onset latency of the p wave was 4.15 ms. The peak-to-peak amplitude between the p and n waves was 3.82 μV, and the threshold of the potentials was 130 dB SPL. The mean peak latency of the p and n waves for the four amikacin-treated guinea pigs was 6.18 ms (SD 0.34 ms) and 7.93 ms (SD 0.58 ms), respectively, and the mean onset latency of the p wave was 4.62 ms (SD, 0.23 ms). The mean onset and peak latencies of the p wave did not differ between the control and amikacin-treated groups ($p > 0.05$). The mean threshold of the myogenic potentials was 131.3 dB SPL (SD 4.8 dB SPL).

Vestibular deafferentation group

The ABR in one guinea pig after vestibular nerve section is shown in Figure 3A. The threshold of the ABR in this animal was 95 dB SPL. In another guinea pig, the threshold of the ABR was 90 dB SPL, postoperatively. In the remaining two guinea pigs, no ABR wave was recorded at a sound

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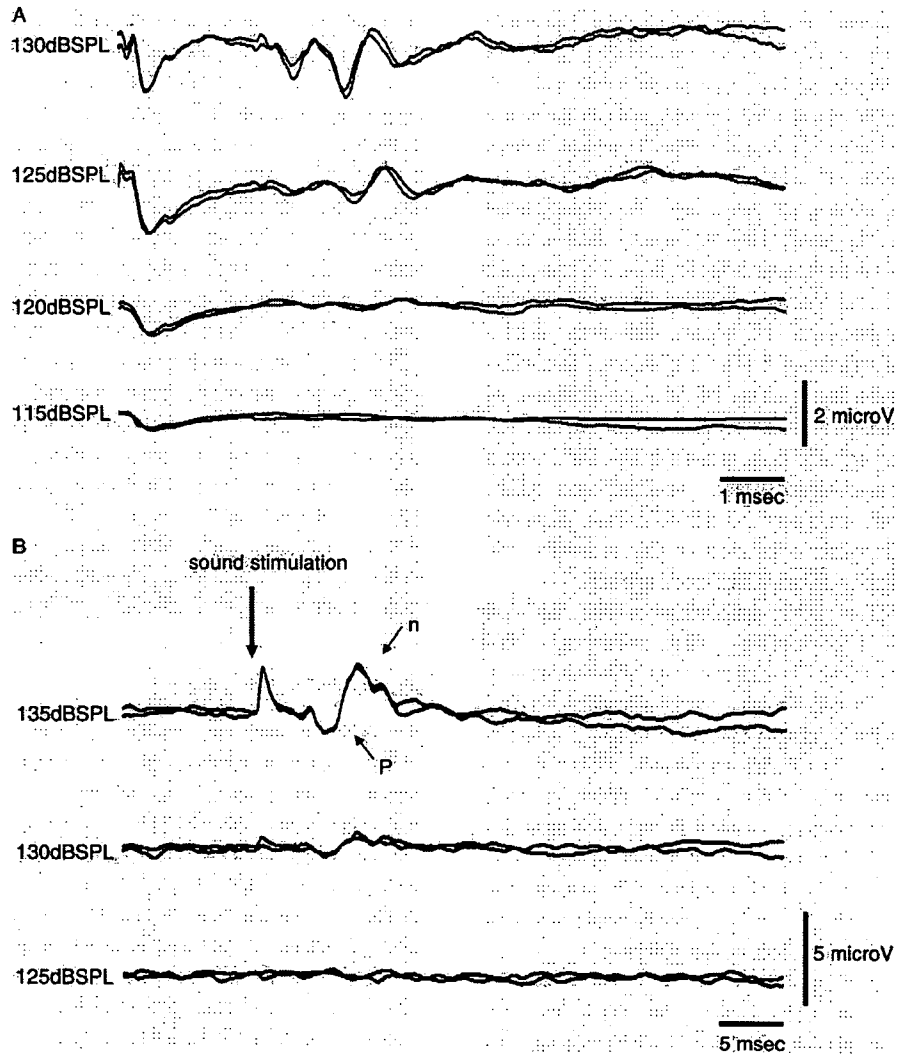

Figure 2. Waveform of the ABR and sound-evoked myogenic potentials on the SM in an amikacin-treated guinea pig (GP11). (A) The threshold of the ABR was 125 dB SPL. (B) The threshold of the sound-evoked myogenic potentials was 130 dB SPL.

stimulation of 135 dB SPL. With respect to the sound-evoked myogenic potentials on the SM, no evoked potentials of short latency were observed in any of the four guinea pigs after vestibular nerve section (Figure 3B).

Discussion

In this study, we investigated sound-evoked myogenic potentials on the SM in guinea pigs. When a brief intense sound at 135 dB SPL was applied, the potentials showed a biphasic waveform within 10 ms after sound stimulation, and the peak latency of the first positive wave was 6.22 ms. The threshold of the potentials was 67 dB SPL higher than that of the ABR. Whereas the myogenic potentials disappeared after vestibular deafferentation, neither the waveforms nor threshold of the potentials were influenced by amikacin administration. Therefore, myogenic potentials of the SM in the guinea pigs originate from the vestibular end organ.

In the inferior branch of the vestibular nerve, the threshold of click-evoked responses is 60 dB SPL greater than that of the ABR [12], and in the vestibular nucleus (lateral vestibular nucleus), the difference in threshold between vestibular and cochlear responses has been shown to be 50–120 dB SPL [10]. In the cervical spinal cord of amikacin-treated guinea pigs, click-evoked potentials have a 90–100 dB SPL higher threshold than that of the ABR [13,14]. These results indicate that sound-evoked vestibular potentials have a higher threshold than responses originating from the cochlea. In this study, sound-evoked myogenic potentials on the SM were 70 dB SPL greater than the threshold of the ABR, consistent with previous reports.

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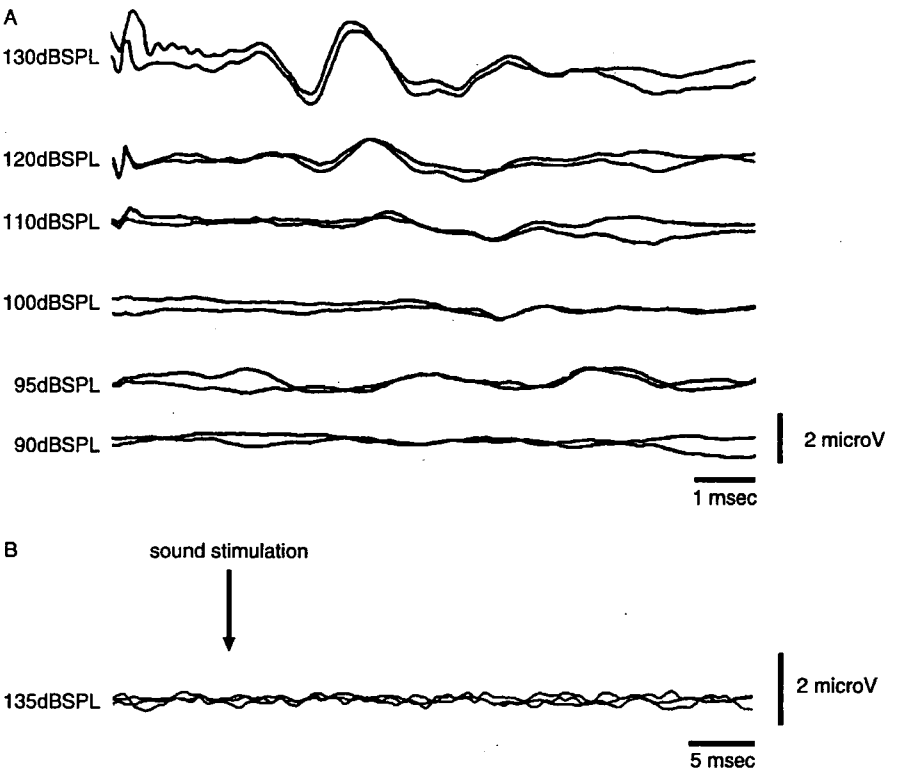

Figure 3. Waveform of the ABR and sound-evoked myogenic potentials on the SM in a guinea pig (GP15) after a vestibular nerve section. (A) The threshold of the ABR was 95 dB SPL. (B) No myogenic potentials were observed.

In amikacin-treated guinea pigs, the threshold of the ABR was increased to 126 dB SPL, 64 dB SPL above that in normal guinea pigs. In contrast, there was only a small difference in the threshold of the myogenic potentials between the two groups, the threshold of the myogenic potentials in the amikacin-treated group was 131 dB SPL, whereas that in the normal group was 128 dB SPL. Therefore, the origin of the myogenic potentials differed from that of the ABR. Intramuscular administration of amikacin is reported to destroy cochlear cells but not vestibular hair cells in guinea pigs [10,11], indicating that the origin of the myogenic potentials is not the cochlea but vestibular end organs.

The dorsal half of the vestibulocochlear nerve was transected in four guinea pigs. In two of the four animals the threshold of the ABR was 30–35 dB SPL higher than that in normal guinea pigs, whereas the other two guinea pigs showed no ABR. The inferior vestibular nerve is located close to the cochlear nerve, and surgical manipulation during vestibular nerve section may have slightly damaged the cochlear nerve. However, myogenic potentials were eliminated in all four guinea pigs, indicating that the pathway for these potentials is via the vestibular nerve.

Motoneurons of the SM (the spinal tract of the accessory nucleus) have a common pattern of vestibulocollic input: excitation from the three contralateral ampullary and utricular nerves and inhibition from the three ipsilateral ampullary, utricular, and saccular nerves via the ipsilateral MLF [15–17]. Both the excitatory and inhibitory vestibulocollic pathways have been described as disynaptic. Therefore, sound-evoked myogenic potentials are thought to be produced by a pathway consisting of at least four synapses: (1) vestibular hair cells to the vestibular nerve, (2) the vestibular nerve to the vestibular nucleus, (3) the vestibular nucleus to a motoneuron of the SM, and (4) the neuromuscular junction between the accessory nerve and the SM. In cats, click-evoked spike potentials in the ventral part of the vestibular nucleus appear with an onset latency of 0.9 ms [17,18], and spike potentials following click stimulation were also recorded in the spinal cord at levels C3–C6 with a peak latency of 4.9–5.1 ms [19]. Motoneurons of the SM are located in the anterior horn of the spinal cord at levels C3–C6. In cats, the duration of peripheral conduction of the accessory nerve to the SM was estimated to be at least 1.1–1.6 ms, according to the latency of the antidromic potentials of the motoneurons of the accessory nerve [20] and to the synaptic delay of the

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neuromuscular junction between the accessory nerve and the SM. The conduction period from vestibular end organs to the SM in guinea pigs should be shorter than the value described above (6.0–6.7 ms), because of the relatively small size of guinea pigs as compared with cats. The onset latency of sound-evoked myogenic potentials on the SM observed in this study (4.9 ms) was as expected, judging from the diameter of the scalp and length of the neck.

Conclusion

The present study showed that a brief intense sound evoked short-latency, high-threshold, and biphasic myogenic potentials on the SM of guinea pigs, which were eliminated by vestibular deafferentation but present after selective cochlear toxicity. Therefore, sound-evoked myogenic potentials on the SM in the guinea pigs originate in vestibular end organs not the cochlea.

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Effects of vestibular nerve section on sound-evoked myogenic potentials in the sternocleidomastoid muscle of monkeys

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Abstract

Objective: The aim of this study was to elucidate the neural pathway for sound-evoked myogenic potentials (SEMPs) in monkeys with characteristics similar to those of vestibular evoked myogenic potentials in humans.
Methods: Six macaque monkeys were examined. The effects of total and selective vestibular nerve section on the SEMPs were evaluated in three monkeys.
Results: After total vestibular nerve section, the SEMPs and caloric nystagmus were eliminated, and the auditory brainstem response remained. After selective superior vestibular nerve section, the SEMPs remained, but caloric nystagmus was eliminated.
Conclusions: The inferior vestibular nerve comprises a neural pathway for SEMPs in monkeys.
Significance: SEMP in monkeys may provide a model of human VEMPs.
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Keywords: Sound-evoked myogenic potentials (SEMPs); Sternocleidomastoid muscle; Macaque monkey; Vestibular nerve section

1. Introduction

The vestibular organ is stimulated by intense sound in pigeons (Wit et al., 1984), guinea pigs (Cazals et al., 1980, 1987; Didier and Cazals, 1989), rats (Sakakura et al., 2003), cats (McCue and Guinan, 1994, 1997), and squirrel monkeys (Young et al., 1977). In humans, sound-evoked myogenic potentials (SEMPs) have been recorded in the sternocleidomastoid (SCM) muscle, and have been described as vestibular evoked myogenic potentials (VEMPs) because they are eliminated by vestibular nerve section. VEMPs can be recorded in patients with profound sensory hearing loss (Colebatch and Halmagyi, 1992; Colebatch et al., 1994; Shojaku et al., 1996, 2000).

In macaque monkeys, intense sound can evoke myogenic potentials with a short-latency, biphasic waveform in the SCM (Tsubota et al., 2006). The characteristics of these SEMPs are similar to those of VEMPs in humans. However, it is not clear whether SEMPs constitute a vestibular response, and if so, which branch of the vestibular nerve conveys the SEMPs. To clarify these issues, the post-operative effect of the SEMPs in the SCM in monkeys was evaluated after vestibular nerve section.

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2. Materials and methods

Six macaque monkeys (Macaca fuscata, $n = 3$; Macaca mulatta, $n = 3$), aged 10- to 23-years-old and weighing 5.8–9.5 kg, were used to record the SEMPs and auditory brainstem response (ABR) in the present study. Three were subjected to vestibular nerve section. In two monkeys, the superior and inferior vestibular nerves were transected, and in a third, the superior vestibular nerve was transected. Between 2 and 4 weeks after vestibular nerve section, SEMPs and ABR were recorded. All animal procedures were approved by the Animal Experimental Committee of the University of Toyama. Some of the data were presented in our previous study (Tsubota et al., 2006).

The detailed recording procedures are described in our previous report (Tsubota et al., 2006). In brief, for SEMP recordings, a pair of surface electrodes (Vitrode V, Nihon Kohden Corp., Tokyo, Japan) was applied over the SCM of each monkey under ketamine hydrochloride (3 mg/kg, intramuscularly) (Sankyo Co. Ltd., Tokyo, Japan) and medetomidine hydrochloride (50 μg/kg, intramuscularly) (Orion Corp., Espoo, Finland) anesthesia. Active and reference electrodes were located on the upper half and sternal head of the SCM muscle of each monkey, respectively. A grounding electrode was attached to the forehead. Once the animal was fully awake, SEMP recording was initiated. Each animal sat on the primate chair and rotated its head toward the contralateral side of the sound stimulation. To obtain clear SEMP responses, the activation of the SCM muscle is necessary. Therefore, in order to induce contraction of the SCM muscle, the animals were trained to receive a small reward (jelly beans) by rotating their head toward the contralateral side in response to sound stimulation to contract the unilateral SCM muscle. We monitored the background electromyogenic (EMG) activity of the tested SCM continuously to monitor muscle tension during the experiment. Alternating clicks (0.1 ms duration, 5 Hz repetition rate) were generated with a Neuropack Σ (Nihon Kohden Corp.) and delivered unilaterally to the external ear canal via an earphone. White masking noise of an intensity 30 dBSPL less than the click stimulating sound was delivered to the contralateral ear. EMG responses were initially low-cut filtered below 5 Hz and then amplified and finally high-cut filtered over 1.5 kHz. After triggering by the onset of the auditory stimuli, 200 consecutive responses were averaged to construct evoked myogenic potentials using both the Neuropack Σ and Mac/Lab systems (AD Instruments Pty. Ltd., Castle Hill, NSW, Australia).

For ABR recordings, surface electrodes were attached to the vertex (active electrode) and bilateral earlobes (reference electrodes) under ketamine hydrochloride (5 mg/kg, intramuscularly) and medetomidine hydrochloride (50 μg/kg, intramuscularly) anesthesia, and a grounding electrode was mounted to the forehead. Under anesthesia, alternating intense clicks, generated by the 0.1 ms duration of the electrical pulse to the insert earphone, and at a stimulation rate of 10 Hz were delivered to the ear. The responses were band-pass filtered between 100 and 3000 Hz, and 1000 consecutive responses were averaged.

To calibrate the intensity of the sound stimulation from the ear phone during SEMP and ABR recordings, the peak equivalent sound pressure levels were measured using by a 2-cc coupler and an attached sound level meter (Model NA-20, Rion Co. Ltd., Tokyo, Japan). The threshold of the SEMP and ABR was defined as the minimum intensity at which a reproducible waveform of at least a double-trace recording could be identified by visual inspection.

To record caloric nystagmus, 2 weeks before the experiment, a head-restraining device (U-shaped plastic plate) was anchored with dental acrylic cement to stainless steel bolts inserted into keyhole slots in the skull under sodium pentobarbital anesthesia (35 mg/kg, intramuscularly) (see Matsumura et al., 1999) and aseptic surgical conditions. The head-restraining device was able to attach to the stereotaxic frame for neurophysiologic experiments set on the primate chair. When we record the caloric nystagmus, the monkey's head was fixed in the primate chair using by this head-restraining device. The monkey's body was able to move freely in the primate chair. To record caloric nystagmus, monkeys were fully awake and maintained in the primate chair in the dark and the primate chair was tilted 60° backward. Horizontal eye movements were recorded by surface electrodes placed at the canthus of each eye. The ground electrode was attached to the forehead. Recordings were obtained with a 2-channel electrooculographic recorder (Chart 5.0 Systems and MacLab 8S, AD Instruments). The first channel recorded horizontal eye movements with a time constant of 3.0 s, and the second channel recorded the slow-phase velocity of the caloric nystagmus with a time constant of 0.03 s. Each ear was irrigated with 20 ml of 45 °C water or 10 °C water at a rate of 1 ml/s. The maximum slow-phase velocity of the caloric nystagmus was measured.

For vestibular nerve section, monkeys were tranquilized with ketamine hydrochloride (5 mg/kg initially, then 3 mg/kg every hour, intramuscularly) and medetomidine hydrochloride (100 μg/kg initially, then 50 μg/kg every hour, intramuscularly). They were intubated and anesthetized with O_2/N_2O, delivered with a respirator. Monkeys were immobilized with pancuronium bromide (Sankyo Co. Ltd.). Body temperature was maintained at 37 °C with a heating pad. During surgery, electrocardiogram, respiratory rate, end-tidal partial pressure of carbon dioxide, percutaneous arterial oxygen saturation, and blood pressure were monitored continuously. A 5% glucose solution was infused through the femoral or radial vein. Vestibular nerve sectioning was performed by two neurosurgeons (NH and MK). The entire vestibular nerve was transected in two monkeys by a posterior cranial fossa approach or by a middle cranial fossa approach, and selective superior nerve transection was performed in one monkey by a middle cranial fossa approach. ABRs were monitored during surgery.

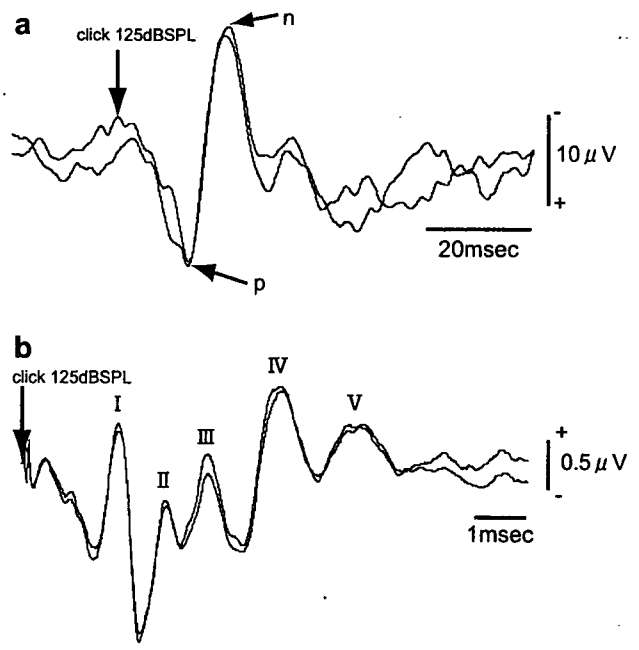

Fig. 1. Sound-evoked myogenic potential (SEMP) and auditory brainstem response (ABR) recordings from a normal monkey. (a) The positive (P) and negative (N) peaks of the SEMP recordings indicate the first positive wave and the subsequent negative wave, respectively. The arrow indicates the onset of the click. (b) ABR recordings. The arrow indicates the onset of the click.

3. Results

SEMPs and ABRs were recorded from 10 ears of 6 monkeys. Representative recordings from one monkey are shown in Fig. 1. The average P latency in the 10 ears was 12.2 ± 2.3 ms, and the average N latency was 20.8 ± 2.7 ms. The average P–N amplitude was 18.8 ± 12.4 μV, and the average SEMP threshold was 103.3 ± 5.0 dBSPL. With respect to ABRs, when an intense click of 125 dBSPL was applied, five waves were identified. The average ABR threshold in the 10 ears was 50.0 ± 9.3 dBSPL.

The effects of total vestibular nerve section on the SEMPs and ABRs in one monkey are shown in Fig. 2. On the sectioned side, SEMPs were eliminated, but ABRs remained, and the ABR threshold was 95 dBSPL. On the intact side, the shape of ABR was changed, but threshold was within normal limits (55 dBSPL).

The effects of total vestibular nerve section on the SEMPs and caloric nystagmus in another monkey are shown in Fig. 3. On the intact side, the maximum slow-phase velocity of the caloric nystagmus was 54.6°/s in response to cold water irrigation and 34.2°/s in response to hot water irrigation. On the sectioned side, SEMPs and caloric nystagmus were eliminated. The effects of selective superior vestibular nerve section on the SEMPs and caloric nystagmus are shown in Fig. 4. On the sectioned side, when an intense click of 125 dBSPL was applied, the P and N latencies were 14.5 and 23.9 ms, respectively, and the P–N amplitude was 14.4 μV. Caloric nystagmus was eliminated.

4. Discussion

SEMPs in the SCM in monkeys had a higher threshold than did auditory responses of cochlear origin (Tsubota et al., 2006). This is similar to VEMPs in humans, but it is not clear whether SEMPs could be attributed exclusively to responses mediated by the vestibular nerve. In this study, SEMPs were eliminated but ABRs remained after total vestibular nerve section, indicating that the SEMPs are conveyed via the vestibular nerve and not the cochlear nerve, as in guinea pigs (Shojaku et al., 2007). Short-latency biphasic myogenic potential on the SCM muscle,

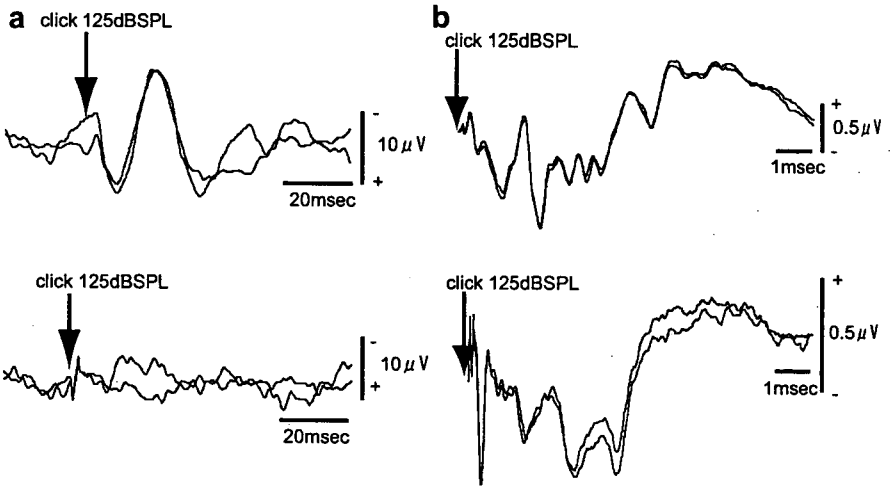

Fig. 2. SEMP and ABR recordings from one monkey after total vestibular nerve section. (a) SEMP recordings. (b) ABR recordings. Upper row, intact side. Lower row, sectioned side. SEMPs were eliminated, but ABRs remained on the sectioned side.

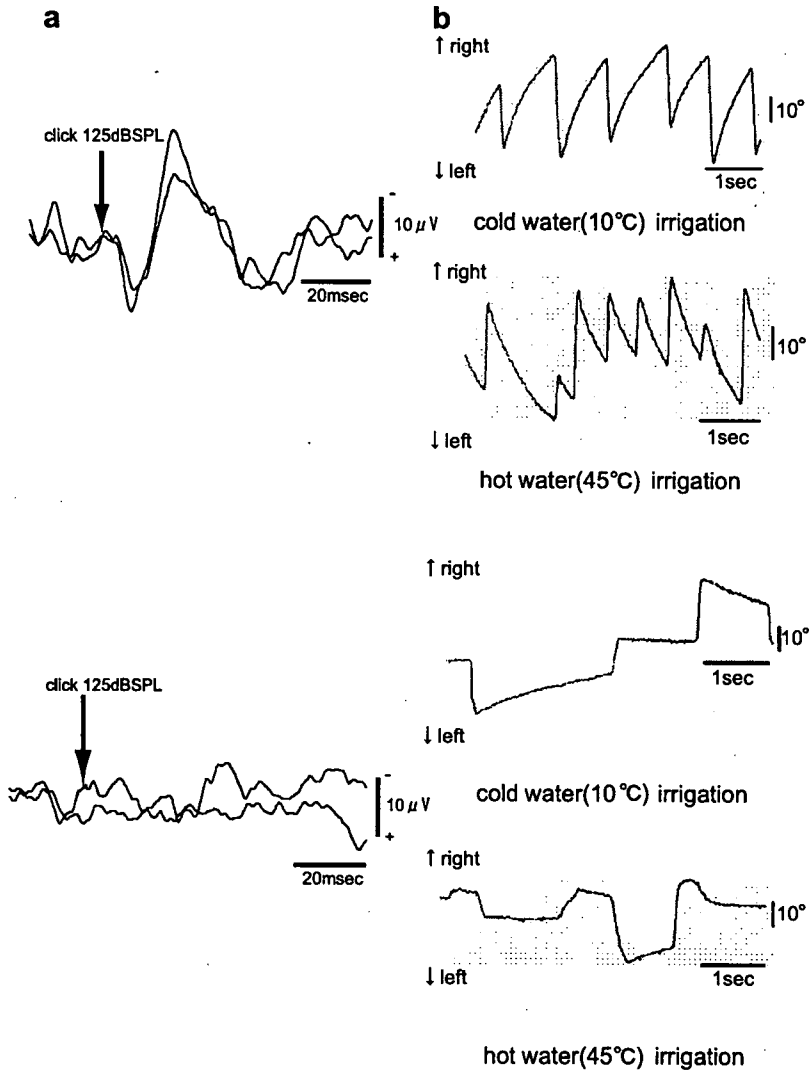

Fig. 3. SEMPs and caloric nystagmus in another monkey after total vestibular nerve section. (a) SEMP recordings. (b) Caloric nystagmus recordings. Upper row, intact side. Lower row, sectioned side. Caloric nystagmus was induced by cold and hot water. SEMPs were normal, but caloric nystagmus was absent on the sectioned side.

with higher thresholds than ABR, was eliminated by vestibular deafferentation, but was not eliminated by selective cochlea toxicity induced by an amikacin injection (Shojaku et al., 2007).

The horizontal semicircular canal is stimulated by caloric stimulation in the sitting position with the head tilted 60° backward. The afferent nerves of the horizontal and anterior semicircular canal, utriculus, and some of the nerve fibers from the sacculus constitute the superior vestibular nerve, whereas most fibers from the sacculus and the posterior semicircular canal comprise the inferior vestibular nerve. After selective superior vestibular nerve section, the SEMPs remained, but caloric nystagmus was eliminated. These findings indicate that the SEMPs are conveyed via the inferior vestibular nerve.

The saccular bundle of the inferior vestibular nerve is known to respond to intense sound in several mammalian species. Young et al. (1977) reported that the saccular afferents were more sensitive to sound than other vestibular fibers in squirrel monkeys. Cazals et al. (1980) reported a loss of acoustic response in guinea pigs after complete cochlear and vestibular hair cell destruction but did observe acoustic responses in cases of partial destruction with preservation of the saccular sensory epithelium. Didier and Cazals (1989) and Murofushi et al. (1995) reported that most acoustic responses of the saccule were conveyed via the inferior vestibular branch of the eighth nerve in guinea pigs. In cats, McCue and Guinan (1994) reported that acoustically responsive afferents innervate the saccule. Thus, it is possible that the origin of SEMPs in monkeys is the sacculus that innervates the inferior vestibular nerve. Further studies, for example, of the effect of singular neurectomy, that is, transcanal posterior ampullary nerve transection (Gacek, 1985), on SEMPs, are necessary.

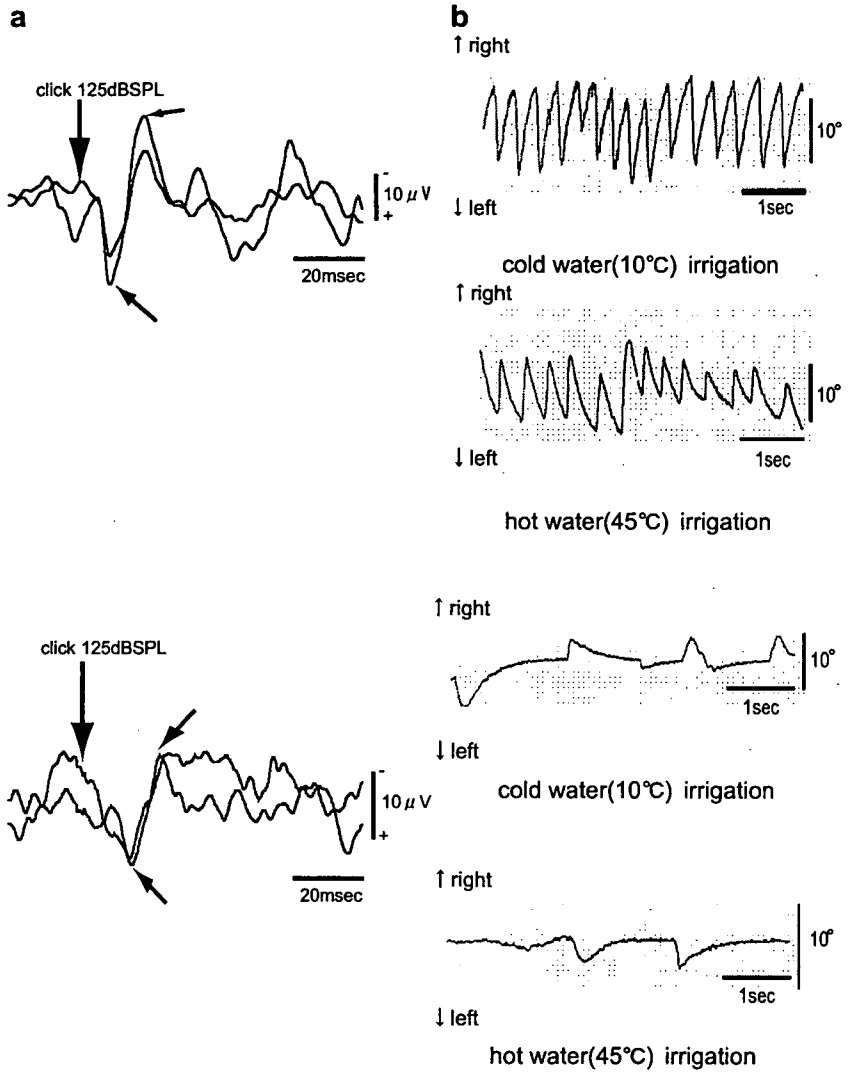

Fig. 4. SEMPs and caloric nystagmus in a monkey after selective superior vestibular nerve section. (a) SEMP recordings. (b) Caloric nystagmus recordings. Upper row, intact side. Lower row, sectioned side. SEMPs remained on the sectioned side as well as the intact side. However, caloric nystagmus was induced only on the intact side.

Dissociation between caloric nystagmus and VEMPs has been documented in humans. Shojaku et al. (1997) reported two cases of acoustic neuroma in which VEMPs were evaluated. In the first case, VEMPs were normal, but severe canal paresis was recorded in the caloric test. In the second case, the peak VEMP latencies of p13 and n23 were delayed, but caloric nystagmus was within normal limits. Murofushi et al. (1998) and Wang et al. (2005) also reported dissociation between VEMPs and caloric nystagmus. Halmagyi et al. (2002) reported that VEMPs in the acute vestibular neuritis were normal but that caloric nystagmus was absent in some patients. Magliulo et al. (2003) reported preservation of the VEMP but not of caloric nystagmus in a patient after resection of a vestibular neurinoma involving the superior but not the inferior vestibular nerve. The origin of caloric nystagmus is fluid motion in the horizontal semicircular canal. Therefore, it is speculated that VEMPs are conveyed via the inferior vestibular nerve. In the present study, SEMP characteristics in intact as well as in transected animals were similar to VEMP characteristics in humans, suggesting that monkey SEMPs may provide a model of human VEMPs. In humans, several investigators (Townsend and Cody, 1971; Murofushi et al., 2003) postulated that the VEMP originates in the saccule. Basta et al. (2005) reported that electrical stimulation of the inferior vestibular nerve during surgery produces VEMP-like myogenic potentials in the SCM. Future studies of this monkey VEMP model will involve more selective inferior vestibular neurectomy and saccular nerve and posterior semicircular nerve section to further elucidate the origin of VEMPs.

In the present study, the latency of wave I of the ABR 75 dB above the threshold was 1.8 ms. The latency of wave I of the ABR 70 dB above the threshold in the Japanese monkey is 1.6 ms (Kamada et al., 1991), whereas that in the rhesus monkey is 1.38 ms (Allen and Starr, 1978). In both studies, the supra-aural earphone was used. In the present study, we used insert earphones, in which the latency delay varies from 0.8 to 1 ms (Van Campen et al., 1992).

In the present study, the ABR remained after total vestibular nerve section. However, the threshold and shape of the ABR were changed on the sectioned side. On the intact side, shape of the ABR was changed, but the threshold was within normal limits. The function of the cochlear nerve appeared to be somewhat compromised in response to the surgery.

In conclusion, the inferior vestibular nerve comprises a neural pathway for SEMPs in monkeys. Therefore, SEMP in monkeys may provide a model of human VEMPs.

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