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Existence of Possible Functional Interaction between the Saccule and the Posterior Semicircular Canal in Humans

An Evaluation Using VEMPs

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Key Words
Evoked potentials · Human vestibulo-ocular reflex · Otolith · Saccule · Semicircular canal · VEMP · Vestibular labyrinth · Vestibulum

Abstract
The purpose of this study was to determine the effects of stimulation of the vertical semicircular canals on vestibular evoked myogenic potentials (VEMPs). VEMPs were recorded in 14 subjects seated with their heads and necks tilted 120° forward on the interaural axis. The head was rotated 45° to the left or right from the sagittal plane; an angular acceleration around the earth's vertical axis was then provided. When the posterior semicircular canal (PSCC) of the recording side was excited, the rotation was defined as 'ipsilateral rotation', and the opposite rotation was defined as 'contralateral rotation'. The background muscle activity-corrected p13–n23 amplitude (CA) in the ipsilateral rotation was significantly smaller than CAs in the static state and the contralateral rotation. Functional interaction between the saccule and the PSCC could be detected.

Introduction

The vestibular labyrinth, which is composed of the semicircular canals (SCCs) and the otolith organs, serves as a sensory organ for angular and linear motions. The SCCs respond to angular accelerations, whereas the otolith organs respond to linear accelerations. In the SCC system, the lateral SCC (LSCC), the anterior SCC (ASCC), and the posterior SCC (PSCC) are at almost right angles to one another, and the system can sense angular acceleration in all directions. The directions for excitatory and inhibitory inputs in the PSCC on one side are opposite to those in the ASCC on the other side. In the otolith organs, the saccule mainly senses vertical linear acceleration and the utricle mainly senses horizontal linear acceleration in an upright posture. In diverse polarization of the macula, the otolith organs operate as multidirectional linear accelerometers.

Animal studies using selective electrical stimulation of individual nerve branches have demonstrated signal convergence from the different SCC and otolith organ receptors onto single vestibular nucleus (VN) neurons [Markham and Curthoys, 1972; Sato et al., 2000; Searles and Barnes, 1977; Uchino et al., 1997, 1999; Zakir et al., 2000; Zhang et al., 2001, 2002]. Studies using natural vestibular stimulation have also revealed that angular and linear acceleration signals interact when they are simultaneously

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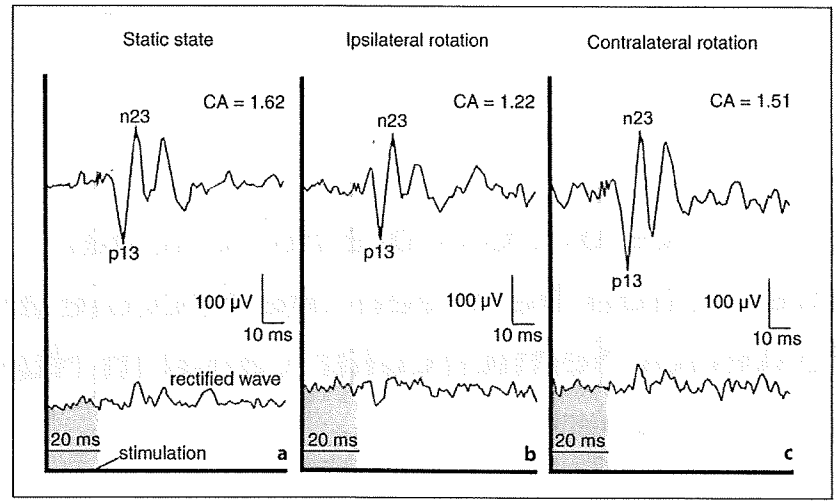

Fig. 1. An example of a VEMP in a 30-year-old man in the static state, ipsilateral rotation and contralateral rotation. The conditions are explained in the 'Methods'. The upper trace represents VEMP recording (unrectified). The lower trace represents rectified muscle activities recorded simultaneously. The mean background amplitude was an integral of the rectified potentials during a prestimulus period of 20 ms (shaded area), divided by 20 (ms). CA was defined as a ratio of the amplitude of p13–n23 to mean background amplitude.

applied to the head [Angelaki and Hess, 1996; Angelaki et al., 1999; Curthoys and Markham, 1971; Gresty et al., 1987; Kasper et al., 1988; McCrea and Chen-Huang, 1999; Sargent and Paige, 1991; Telford et al., 1996].

In human studies, Karino et al. [2005] examined functional interaction between the saccule and the LSCCs using vestibular evoked myogenic potentials (VEMPs), which represent myogenic responses of the sternocleidomastoid muscle (SCM) evoked by acoustic stimulation delivered to the saccule, transmitted mainly via the inferior vestibular nerve. No functional interaction between the saccule and the LSCCs was detected [Karino et al., 2005].

Previous studies showed that the percentage of VN neurons that received convergent inputs from the vertical SCCs (VSCCs) and the saccular nerves was higher than from the LSCC and the saccular nerves [Sato et al., 2000; Zhang et al., 2001, 2002]. This implies that convergent inputs from the VSCCs and the saccular nerve pairs might play a more important role than those from the LSCC and the saccular nerve pairs.

We hypothesized that functional interaction between the saccule and the VSCCs might exist in humans and investigated the effect of angular acceleration, which naturally stimulated VSCCs on VEMPs.

Methods

Subjects

Fourteen normal volunteers (12 men and 2 women; mean age 31.4 years, range 25–42) without a previous history of otological or neurological diseases were enrolled. The study was approved by the local ethics committee, and informed consent was obtained from each subject.

VEMP Recording

Electromyographic activity was recorded from a surface electrode placed on the upper half of each SCM, with a reference electrode on the side of the upper sternum and a ground electrode on the nasion. During the recording, the subjects were instructed to twist their neck to activate the SCM and to maintain the muscle activities at a constant level, as described later. The electromyographic signal from the stimulated side was amplified and band-pass filtered (20–2000 Hz). The stimulation rate was 5 Hz, and the analysis time was 100 ms (–20 to 80 ms). Short tone bursts of 500 Hz [95 dB normal hearing level, 135 dB SPL (peak value); rise/fall time, 1 ms; plateau time 2 ms] were presented to each ear through headphones (type DR-531; Elega Acous. Co. Ltd., Tokyo, Japan). The latencies and amplitudes of the first positive-negative peaks (p13–n23) of the VEMP were evaluated. To eliminate the effect of the variance of muscle activities, we calculated the mean background amplitude from the integral of rectified background activities during a prestimulus period of 20 ms, as described previously [Colebatch et al., 1994; Ito et al., 2007; Karino et al., 2005; Murofushi et al., 2007]. The corrected amplitude (CA) of VEMP was defined as a ratio of (amplitude of p13–n23)/(mean background amplitude) in each run (fig. 1a–c). The normalized VEMP amplitude (dimensionless) was employed for comparison between conditions with or without a stimulation of SCCs.

Stimuli and Procedures

Angular acceleration was provided by a rotatory chair mounted on a computer-controlled direct-drive motor (S-II; Nagashima Medical Instruments Co. Ltd., Tokyo, Japan). During VEMP recording, the subjects were seated on the chair with their heads and necks tilted 120° forward on the interaural axis, as shown in figure 2a–c, and their heads were rotated 45° to the left or right from the sagittal plane. The subjects rotated their heads in the direction opposite to the sound-stimulated side to activate the SCM. As

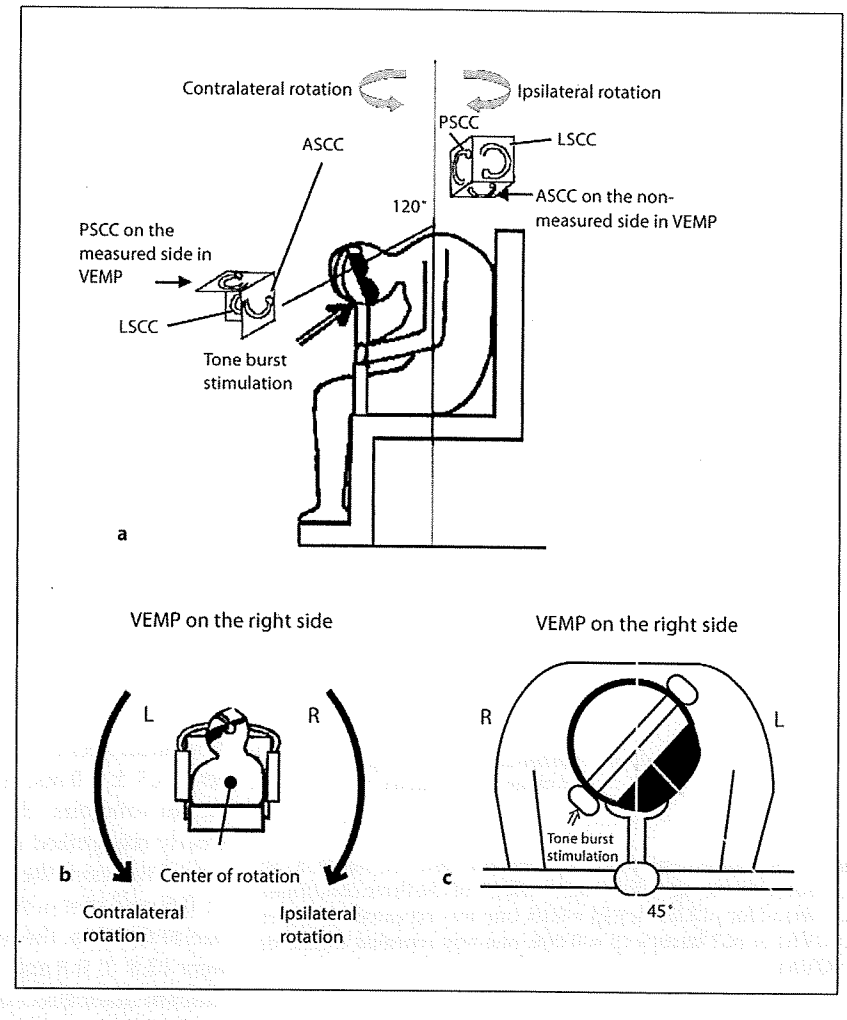

Fig. 2. Schematic illustration of the setup. During VEMP recording, subjects were seated on a chair with their head and neck tilted 120° forward on the interaural axis, and their head rotated 45° to the left or right from the sagittal plane (**a–c**). The subjects rotated their heads in a direction opposite to the sound-stimulated side to activate the SCM (**a**). The PSCC on the measured side in VEMP and the ASCC on the non-measured side, which were parallel, were perpendicular to the rotational axis (**a**) When the right ear and the SCM were selected for recording, clockwise rotation from the view over the subject was defined as 'ipsilateral rotation', and counterclockwise rotation from the same view was defined as 'contralateral rotation' (**a**, **b**). When the left ear and SCM were selected, counterclockwise rotation from the view over the subject was defined as 'ipsilateral rotation', and clockwise rotation from the same view was defined as 'contralateral rotation'.

shown in figure 2a–c, when the head of the subject was tilted 120° and rotated 45° to the side on which VEMPs were not measured, the PSCC on the measured side and the ASCC on the non-measured side, which were parallel, were perpendicular to the rotational axis. Subjects wore goggles to preserve the dark conditions and were instructed to keep their eyes open during the session. When the right ear and SCM were selected for recording, the nose was toward the left; clockwise rotation from the view over the subject was defined as 'ipsilateral rotation', and counterclockwise rotation from the same view was defined as 'contralateral rotation' (fig. 2a, b). When the left ear and SCM were selected, counterclockwise rotation from the view over the subject was defined as 'ipsilateral rotation,' and clockwise rotation from the same view was defined as 'contralateral rotation.' From the static state, the chair was accelerated at 12°/s^2 to a final velocity of 180°/s.

Seven of 14 subjects were tested with VEMPs measured on the right side and the other subjects were tested on the left side.

First, the eye movement of subjects during ipsilateral rotation was monitored by an infrared computer-controlled display camera (Nistamo 21; J. Morita Mfg. Corp., Kyoto, Japan) to check the upbeat nystagmus, which demonstrated that the PSCC of the measured side was excited. Then in the static state, the responses to 70 tone bursts were recorded once in one side of the SCM (prerotatory static VEMP). The first trial in ipsilateral rotation, the first trial in contralateral rotation, the second trial in ipsilateral rotation, and the second trial in contralateral rotation were performed in this order. VEMPs during rotation were acquired by averaging evoked electromyographic signals during 15-second rotations. In the static state, the responses to 70 tone bursts were recorded once (postrotatory static VEMPs). The time interval sufficient to confirm the disappearance of postrotatory nystagmus was interspaced during each session. The average CAs of the pre- and postrotatory static VEMPs were regarded as CAs in the static state. As described above, two trials were administered in each of the ipsilateral and contralateral rotations. The average CAs of

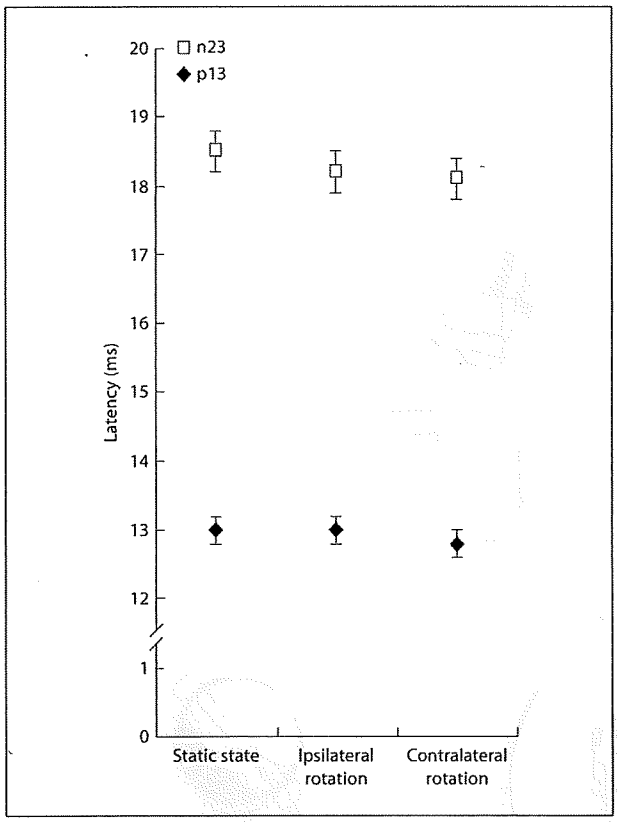

Fig. 3. The results of p13 and n23 latencies. Data are means ± SE of 14 subjects. No significant main effects of the three conditions were found for p13 latency ($p = 0.15$, one-way repeated measures ANOVA) or p23 latency ($p = 0.068$, one-way repeated measures ANOVA).

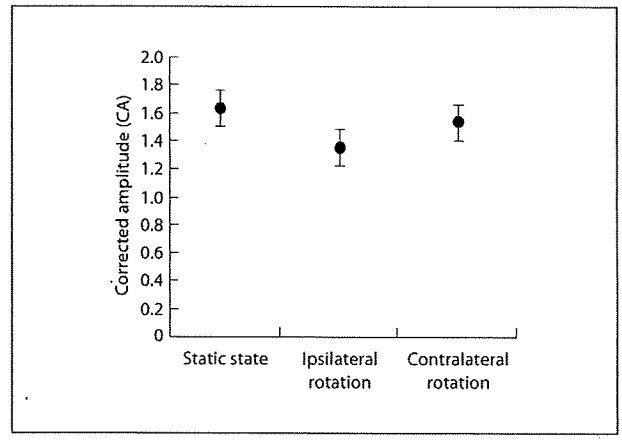

Fig. 4. The results of CAs. Data are means ± SE of 14 subjects. A significant effect of the three conditions was found in CA ($p = 0.0074$, one-way repeated measures ANOVA). Bonferroni's multiple comparison tests confirmed that CA in ipsilateral rotation was significantly smaller than CAs in the static state and contralateral rotation ($p = 0.0021$ and 0.039, respectively).

the first and second trials were regarded as CAs in each direction of rotation.

Data Analysis

The differences in the latencies of p13 and n23 and CAs in three conditions (static state and ipsi-/contralateral rotations) were analyzed by one-way repeated measures analysis of variance (ANOVA). $p < 0.05$ denoted the presence of a statistically significant difference.

Results

Latency of p13 and n23

In the static state on the rotatory chair, the VEMPs of the 14 subjects (the right SCM in 7 subjects and the left SCM in 7) showed distinct peak levels of p13 and n23. The mean latencies ± SD of p13 and n23 were 13.0 ± 0.8 and 18.5 ± 1.0 ms, respectively. In ipsilateral and contralateral rotations, the peak levels of p13 and n23 were clearly recognized similar to the static state. In the ipsilateral rotation, the mean latency ± SD of p13 was 13.0 ± 0.6, and that of n23 was 18.2 ± 1.0 ms. In the contralateral rotation, the mean latencies ± SD of p13 and n23 were 12.8 ± 0.8 and 18.1 ± 1.1 ms, respectively. No significant main effect of the three conditions was found in the latencies of either p13 or n23 by one-way repeated measures ANOVA (fig. 3).

Comparison of CAs

Figure 4 shows a comparison of CA values between the three conditions. In the static state, the mean CA ± SD of the 14 subjects was 1.63 ± 0.47. In the ipsilateral and contralateral rotations, the mean CAs ± SD were 1.35 ± 0.41 and 1.53 ± 0.44, respectively. One-way repeated measures ANOVA showed a significant effect of the three conditions [$F(2, 26) = 5.956$, $p = 0.0074$]. Bonferroni's multiple comparison tests confirmed that the CA in the ipsilateral rotation was significantly smaller than the CAs in the static state and the contralateral rotation ($p = 0.0021$, $p = 0.039$, respectively). In comparison with CAs, the power of ANOVA was 0.85, which showed that the number of subjects was sufficient. In the static state and the ipsi- and contralateral rotations, the mean amplitudes

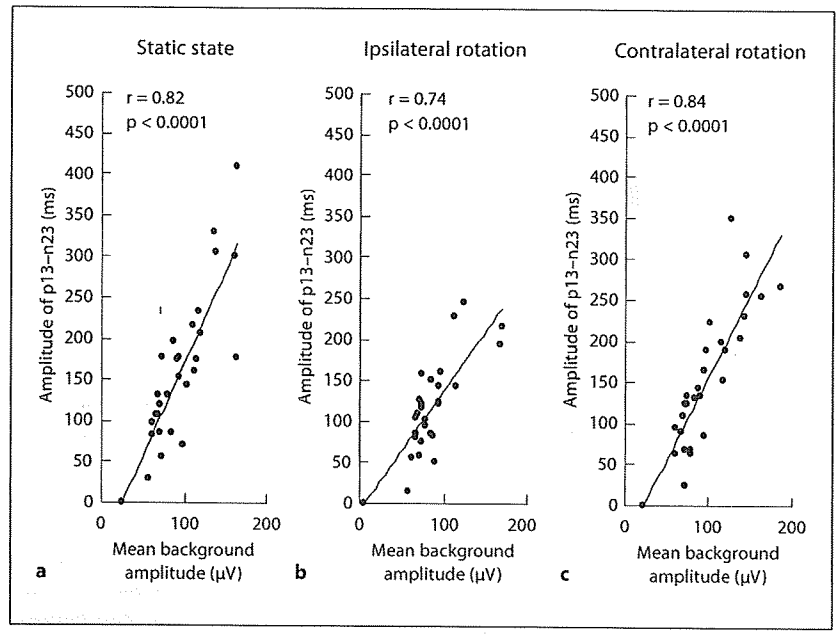

Fig. 5. Correlation between the amplitude of p13–n23 and mean background amplitude. Pearson's correlation coefficients (r) and p values are shown in each scatter plot.

Table 1. The average ± SD of the mean background amplitude and the amplitude of p13–n23 in the static state, ipsilateral rotation and contralateral rotation

	Static state	Ipsilateral rotation	Contralateral rotation
Mean background amplitude, μV	98 ± 32	88 ± 28	101 ± 34
Amplitude of p13–n23, μV	166 ± 88	120 ± 54	159 ± 81

The number of subjects is 14, and each subject was administered two trials of VEMP testing in each condition.

± SD in the 14 subjects were 98.2 ± 28.6, 88.1 ± 27.5, and 100.6 ± 32.1, respectively. One-way repeated measures ANOVA did not show a significant effect of the three conditions [$F(2, 26) = 2.464$, $p = 0.10$].

Validity of CA

There was a significant correlation between the amplitude of p13–n23 and the mean background amplitude in each condition (fig. 5a–c, table 1). These results validated the reliability of CA, which was defined as a ratio of (amplitude of p13–23)/(mean background amplitude).

Discussion

Comparison of CAs

The angular acceleration that causes ampullofugal endolymph flow increases the firing rate of the PSCC and the ASCC nerves. On the other hand, angular acceleration, which causes ampullopetal flow, decreases the firing rate of these nerves. In the ipsilateral rotation of the present study, the firing rate of the PSCC nerve on the measured side in VEMP was increased, and that of the ASCC nerve on the other side was decreased. Contralateral rotation induced inverse effects.

In animal studies, electrical stimulation of the saccular nerve evokes excitatory postsynaptic potentials in VN neurons and then inhibitory postsynaptic potentials in ipsilateral SCM motoneurons, probably via the medial vestibulospinal tract (MVST; fig. 6) [Kushiro et al., 1999]. On the other hand, the saccular nerve has no connections with contralateral SCM motoneurons (fig. 6) [Kushiro et al., 1999]. This finding suggests that the p13–n23 response is referable to the inhibition of SCM muscle unit activities [Colebatch and Rothwell, 2004; Halmagyi et al., 1994] and is in concurrence with VEMPs being mainly evoked in the ipsilateral SCM [Murofushi et al., 2004].

The PSCC nerve has disynaptic inhibitory connections with ipsilateral SCM motoneurons (fig. 6) [Shinoda et al., 1994]. Some VN neurons are antidromically acti-

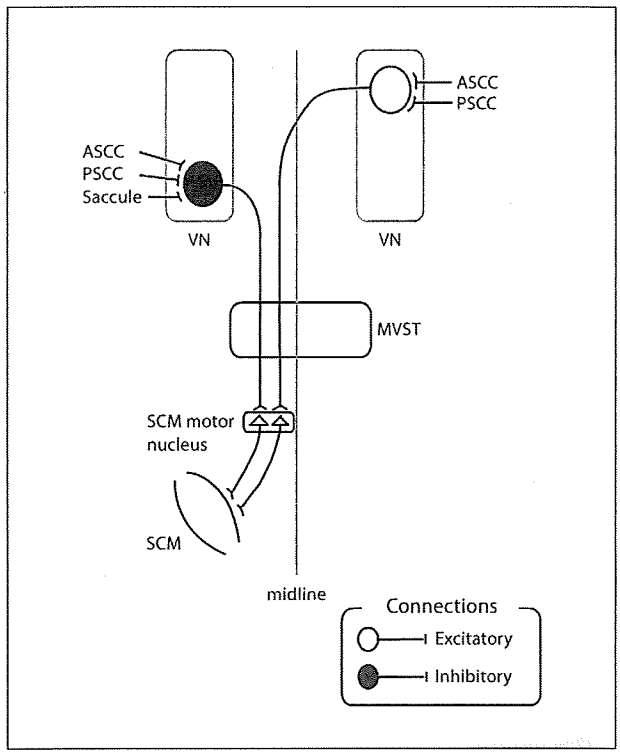

Fig. 6. Schematic illustration of the neural connectivity between the vestibular receptors and the SCM (reference to the ASCC, the PSCC and the saccule). The saccular nerve has disynaptic inhibitory connections with ipsilateral SCM motoneurons via the MVST, but no connections with contralateral SCM motoneurons. The ASCC and the PSCC nerves both have disynaptic inhibitory connections with ipsilateral SCM motoneurons and disynaptic excitatory connections with contralateral SCM motoneurons.

vated by stimulation of the C1–C2 junction in electrophysiological studies, which have been called vestibulospinal (VS) neurons. Of the VS neurons that received inputs from the saccular and/or the PSCC nerve and descended through the MVST, more than half received convergent inputs from both of these nerves, which was demonstrated by selective electrical stimulation of primary vestibular afferent neurons of cats [Sato et al., 2000]. Based on these previous studies, it is conceivable that many VS neurons connecting with the saccular nerve received convergent inputs from the PSCC nerves, eliciting disynaptic inhibitory postsynaptic potentials in the ipsilateral SCM. In other words, VS neurons that received convergent inputs from both the saccular and the PSCC nerves could be involved in the neural pathway of VEMPs; therefore, the input from the PSCC could affect VEMPs. The significant difference in CAs of VEMPs under simultaneous stimulation of the PSCC, as shown in the present study, is consistent with previous studies.

The preceding paper from our group showed no significant difference in CAs between the static state and stimulation of bilateral LSCCs by angular acceleration [Karino et al., 2005]. By selective electrical stimulation of primary vestibular afferents of cats, a relatively small percentage of primary vestibular afferents from the LSCC and the saccule converged on VN neurons [Zhang et al., 2001]. The percentage of VN neurons that received convergent inputs from the PSCC and the saccular nerves was higher than those from the LSCC and the saccular nerves [Sato et al., 2000; Zhang et al., 2001]. The present study was performed with the same acceleration as in the study of Karino et al. [2005], i.e. 12°/s^2 to a final velocity of 180°/s. The results of the CAs revealed that the interaction between the PSCC and the saccule was more prominent than between the LSCC and the saccule.

Sato et al. [2000] demonstrated that excitatory inputs from the PSCC and the saccule connected monosynaptically or polysynaptically with more than 70% of the total convergent VS neurons. The firing rate of the primary vestibular afferents from the PSCC on the measured side in VEMP increases by ipsilateral rotation. In the present study, the CA in ipsilateral rotation was significantly smaller than the CAs in the static state and contralateral rotation. We speculated that excitatory inputs from the PSCC might increase firing independent of tone-burst stimuli and act as a factor disturbing the neural synchrony required for p13–n23, causing a decrease in the CA in ipsilateral rotation.

Contralateral rotation gave inhibitory input from the PSCC; however, no significant difference in CAs was found between the static state and the contralateral rotation. Asymmetrical responses of the SCCs to angular acceleration might be one reason for this finding. Otherwise, the decrease in such independent firing might have no effect on neural synchrony.

The ASCC nerve also has disynaptic excitatory connections with contralateral SCM motoneurons (fig. 6) [Fukushima et al., 1979]. The firing rate of primary vestibular afferents from the ASCC on the non-measured side in VEMP is also affected by angular acceleration. In the present study, there was no significant difference in CAs between the static state and contralateral rotation, and the CA in contralateral rotation was significantly larger than the CA in ipsilateral rotation. If VS neurons receiving input from the ASCC and projecting to contra-

lateral SCM motoneurons were fewer than those projecting to ipsilateral SCM motoneurons, these few connections from the non-measured side in VEMP could not affect VEMPs. Our result might support such an assumption; however, there is not any other electrophysiological knowledge about the quantitative difference between neurons projecting to contralateral SCM motoneurons and those projecting to ipsilateral SCM motoneurons. The possibility of interactions at the SCM motoneuron level cannot be completely excluded.

Angular acceleration could affect muscle contractions of the SCM, leading to a change in the amplitude of p13–n23; however, as we employed CA, which was defined as a ratio of the amplitude of p13–n23 to mean background amplitude, the possible effect on the degree of muscle contractions could be canceled.

We cannot exclude the possibility that the distance of the labyrinth from the rotation axis had an effect as eccentric rotation [Crane and Demer, 1998, 2000; Furman and Baloh, 1992; Gresty et al., 1987; Viirre and Demer, 1996]. When the distance from the axis to the saccule was R (m), the normal acceleration generated in the saccule in ipsilateral rotation was the same both in size and in direction as in contralateral rotation, and the size was $R \times (12 \times \pi/180 \times t)^2 = 0.044R\,t^2$ (m/s^2). The farther the axis of rotation is placed from the saccule, the larger the normal acceleration becomes. In the present study, the distance was approximately 0.3 m and the time it took to reach the maximum was 180/12 = 15 (s); thus, the maximum value of the normal acceleration was 3.0 m/s^2, which was approximately 30% of the acceleration of gravity (9.8 m/s^2). If the normal acceleration were the main factor for the change in CA, the difference in CA between ipsilateral rotation and contralateral rotation could not be explained, while the difference between the static state and the rotational state could. Therefore, the effects on CAs by normal acceleration generated in the saccule were ignorable with regard to the difference between the ipsilateral rotation and contralateral rotation. On the other hand, the tangential acceleration in the saccule in ipsilateral rotation was generated in a direction opposite to contralateral rotation. It was impossible to perform the experiments for the purpose of studying the effects on CAs by the tangential acceleration generated in the saccule in the present experimental system, because the system could not divide the tangential acceleration generated in the saccule from that in the SCC. However, the tangential acceleration generated in the saccule had a constant value and the size was 0.3×12 (°/s^2) $= 0.3 \times \pi/15$ (rad/s^2) = 0.063 (m/s^2), which was only 0.6% of the acceleration of gravity. VEMPs with tone burst stimuli were hardly affected by the directions of gravity in a previous report [Ito et al., 2007]. They measured VEMPs in various directions of gravity, but CAs did not differ significantly. Furthermore, the polarity of hair cells on the saccular macula is not uniform. Therefore, the effects on CAs by the tangential acceleration, which was much smaller than the acceleration of gravity in the present study, could be ignored. Given the size and direction of acceleration, the effects on CAs by the acceleration generated in the saccule were ignorable with regard to the difference between the ipsilateral rotation and contralateral rotation.

Comparison of Latencies

There was no significant difference in the latencies of p13 or n23 in any condition.

In the study of VEMP testing during angular acceleration, Karino et al. [2005] showed that there was no significant difference in the latencies of p13 or n23 between the static state and stimulation of bilateral LSCCs.

The percentage of VN neurons that received convergent inputs from the VSCC and the saccular nerves was higher than those from the LSCC and the saccular nerves according to previous animal studies [Sato et al., 2000; Zhang et al., 2001, 2002]. We had expected that convergent inputs from the VSCC and the saccular nerves might play a more important role than those from the LSCC and the saccular nerves; however, in terms of the latencies of p13 and n23, stimulation by angular acceleration to stimulate the PSCC on the measured side in VEMP and the ASCC on the other side on a plane perpendicular to the rotational axis seems to have no significant influence.

The latency of VEMPs is delayed in diseases which involve retrolabyrinthine lesions such as acoustic neurinoma or multiple sclerosis [Murofushi et al., 2001; Shimizu et al., 2000]. These diseases could affect conduction velocity. We speculated that angular acceleration could affect the number of neurons which fire with synchronization to tone burst stimuli, but could not affect conduction velocity.

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Does migraine-associated vertigo share a common pathophysiology with Meniere's disease? Study with vestibular-evoked myogenic potential

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To clarify if migraine-associated vertigo (MAV) and Meniere's disease (MD) share a common pathophysiology, vestibular-evoked myogenic potentials (VEMP) were measured in 11 patients with MAV, 11 with unilateral MD and eight healthy subjects. As acoustic stimuli, tone bursts (TB; 250, 500, 1000 and 2000 Hz) were presented. In healthy subjects, 500-Hz TB evoked the largest amplitude. To quantify this tendency, 500–1000 VEMP slope was calculated, and 500–1000 VEMP slope was the smallest on the affected side of MD patients. Among the 11 MD patients, five had significantly decreased 500–1000 VEMP asymmetry (shift of the tuning to 1000 Hz). Three of the 11 MAV patients also showed a significantly decreased 500–1000 VEMP slope. This finding suggests that MAV might share a common pathophysiology with MD. In addition to this finding, four of the other eight MAV patients showed prolonged p13 latencies. This suggests that MAV could consist of patients with different lesion sites.

☐ *Vestibular, saccule, migraine, headache, endolymphatic hydrops, tuning*

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Introduction

Patients with migraine often report vertigo/dizziness. The clinical association of migraine with vertigo/dizziness has been supported by several epidemiological studies (1, 2). Migraine-associated vertigo (MAV), migraine-associated dizziness or migrainous vertigo (MV) has been proposed as one of the main clinical entities of balance problems (1–5). However, the pathophysiology of MAV remains to be clarified.

Meniere's disease (MD) is also one of the most common diseases that cause recurrent vertigo attacks. In addition to recurrent vertigo, patients with MD have fluctuating hearing loss, tinnitus, and a sensation of aural fullness (6). Histopathological studies of the temporal bone have revealed endolymphatic hydrops in the affected ears (7–9). Differential diagnosis of MAV from MD is sometimes hard because patients with MAV could have tinnitus and/or aural fullness during vertigo attacks (10), and a controlled study has provided evidence of the association of MD with migraine (11). One might therefore assume that the two conditions, MAV and MD, could share common pathophysiological mechanisms (12).

Vestibular-evoked myogenic potential (VEMP) has been regarded as a vestibulo(sacculo)-collic reflex evoked by acoustical stimulation and applied as a clinical test of the vestibular system (13–15). On the basis of previous reports, the incidence of abnormal VEMP in patients with MD (absence of responses or decreased amplitudes) is considered to be around 40–50% (16, 17). Rauch et al. (18)

reported the alteration of tuning characteristics of VEMP in MD patients. According to previous studies (18–20), the best frequency of VEMP is between 300 and 700 Hz. Rauch et al. (18) reported that, in healthy subjects, the largest amplitude and the lowest threshold were obtained to 500-Hz tone bursts (TB), whereas patients with MD showed less tuning at 500 Hz and shifts of the best frequency to 1000 Hz. Rauch et al. attributed this shift to the change of resonant frequency in the saccule. We assumed that VEMP in patients with MAV could show the same tuning characteristics as those in patients with MD if MAV and MD share common pathophysiological mechanisms. Of course, MAV patients might show other abnormal findings. Concerning VEMPs in patients with migraine or MAV, there are only a few reports (21, 22), which showed decreased amplitudes of VEMP in patients with migraine.

Here, we studied characteristics of VEMP responses in patients with MAV and compared those with patients with MD and healthy subjects

Materials and methods

Subjects

Eleven patients with MAV (two men, nine women, 18~60 years of age, mean 41.3 years), eight healthy volunteers (four men, four women, 30~48 years of age, mean 37.3 years) and 11 patients with unilateral definite MD (three men, eight women, 44~78 years of age, mean 58.2 years) were enrolled. As the diagnostic criteria of definite MD, American Academy of Otolaryngology-Head and Neck Surgery guidelines (1995) (6) were adopted (Table 1). As the diagnostic criteria of migraine, we adopted International Headache Society criteria (23). As the diagnostic criteria of MAV, we used the criteria shown in Table 2, which were processed on the basis of Neuhauser's criteria (12) and Brantberg's criteria (3). Adopting our criteria, patients with associated unilateral hearing loss were excluded in order to differentiate MD clearly. This study was prospective. None of our subjects had conductive hearing loss on either side.

The study was performed according to the Declaration of Helsinki. Informed consent was obtained from each subject. Ethical approval was received from the Tokyo Postal Services Agency Hospital ethics committee.

Table 1 Diagnostic criteria definite Meniere's disease (6)

1. Two or more definitive spontaneous episodes of vertigo ≥ 20 min
2. Audiometrically documented hearing loss on at least one occasion
3. Tinnitus or aural fullness in the treated ear
4. Other causes excluded

Methods

For recording VEMPs, electromyographic (EMG) activity was recorded from a surface electrode placed on the upper half of each sternocleidomastoid muscle (SCM), with a reference electrode on the lateral end of the upper sternum and a ground electrode on the nasion (24). Recording was performed with Neuropack system (Nihon Kohden Co. Ltd, Tokyo, Japan). During the recording, subjects in the supine position were instructed to raise their heads from the pillow to contract the SCM.

All healthy subjects underwent VEMP testing using air-conducted TBs (rise/fall time 1 ms, plateau time 5 ms, 250, 500, 1000 and 2000 Hz), and patients with MD or MAV did VEMP testing using 500-Hz and 1000-Hz TB. Acoustical stimuli were presented through a headphone (Type DR-531; Elega Acous. Co. Ltd, Tokyo, Japan) (25). The sound intensity was 130 dB sound pressure level (SPL) for 500, 1000 and 2000 Hz, but 120 dB SPL for 250 Hz due to the limitation of the device. EMG activities were amplified and bandpass-filtered (20–2000 Hz). The stimulation rate was 5 Hz, and the time window for analysis was 100 ms (–20 to 80 ms). Responses to 25 TB stimuli for each run were averaged. Reproducibility of responses was confirmed by two runs for each frequency. We used the average of two runs as the amplitude of p13-n23 and latencies of p13 and n23 (Fig. 1).

We analysed the amplitude of the first biphasic responses (p13-n23) on the ipsilateral SCM to the stimulated ear (13) and the peak latencies of p13 and n23 (26) (Fig. 1). In order to eliminate the effect of variance of muscle activities, the mean

Table 2 Diagnostic criteria of migraine-associated vertigo in this study

1. Recurrent vestibular symptoms
2. Migraine headache according to the IHS criteria
3. At least one synchronization of vertiginous attack with migraine headache
4. No associated unilateral hearing loss
5. No other disease causing vertiginous attack

IHS, International Headache Society.

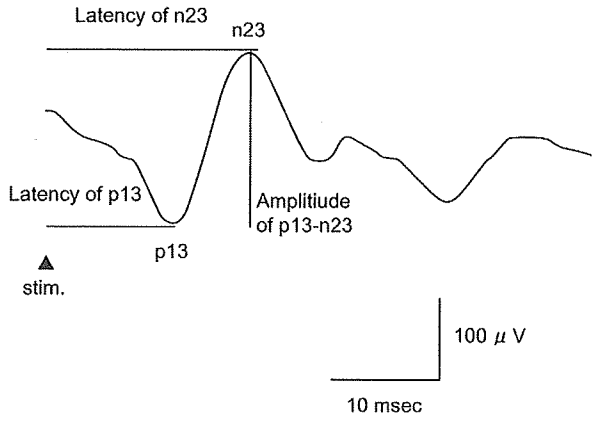

Figure 1 Parameters measured in vestibular-evoked myogenic potentials.

background amplitude was calculated from the integral of rectified background activities during a pre-stimulus period of 20 ms (27, 28). Then corrected amplitudes (CA) were calculated as follows:

$$\text{CA of VEMP} = (\text{raw amplitude of p13-23})/(\text{mean background amplitude})$$

In order to evaluate interaural asymmetry of VEMP responses, interaural VEMP asymmetry was calculated as follows (24):

Interaural VEMP asymmetry $= 100 \times |CAr - CAl| / (CAr + CAl)$ in healthy subjects and patients with MAV, and, in MD patients:

$$\text{Interaural VEMP asymmetry} = 100 \times (CAu - CAa)/(CAu + CAa)$$

where CAr(l) is the corrected amplitude of p13-n23 on the right (left) SCM to the right (left) ear stimulation, CAu(a) the corrected amplitude of p13-n23 on the unaffected (affected) side to the unaffected (affected) side stimulation, and $|CAr - CAl|$ is the absolute value of $(CAr - CAl)$.

In order to compare CA to 500-Hz TB with CA to 1000-Hz TB, 500–1000 slope was calculated as follows:

$$\text{500–1000 VEMP slope} = 100 \times (CA500 - CA1000)/(CA500 + CA1000)$$

where CA500 is the corrected amplitude of p13-n23 to 500-Hz TB, and CA1000 is the corrected amplitude of p13-n23 to 1000-Hz TB.

Therefore, the positive value of 500–1000 VEMP slope indicates the dominancy of VEMP responses in 500 Hz, whereas the negative value is the dominancy in 1000 Hz.

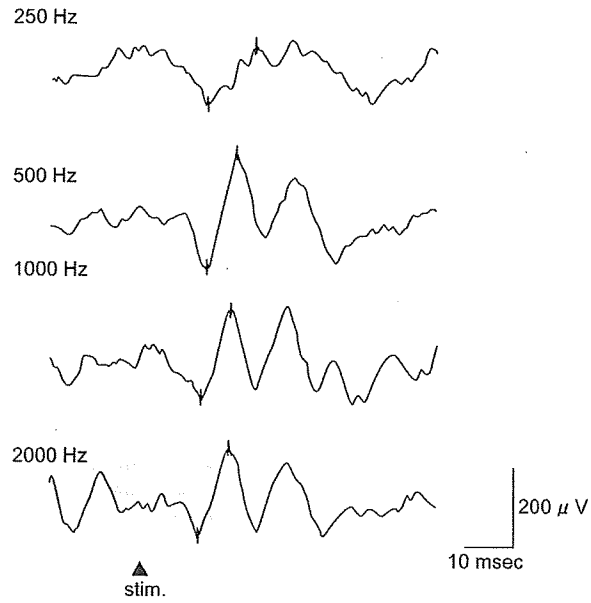

Figure 2 Vestibular-evoked myogenic potentials of a 43-year-old healthy woman (responses on the left side). She showed the largest response to 500-Hz tone bursts among the four frequencies.

Results

VEMPs to TBs in healthy subjects

Both sides of all the healthy subjects showed clear VEMP responses to 500-Hz and 1000-Hz TB. On the other hand, responses to 2000 Hz and 250 Hz were observed in 87% (14/16) and 68% (11/16), respectively. The mean of CA was the largest to 500-Hz TB in this study (Figs 2 and 3 and Table 3).

We calculated interaural VEMP asymmetries to 500-Hz and 1000-Hz TBs because the detection rates of responses to these two frequencies were 100% in healthy subjects. They were 15.4 ± 6.7 (mean ± S.D.) to 500-Hz TB and 21.5 ± 15.4 to 1000-Hz TB. According to these results, the upper limits of the normal ranges of interaural VEMP asymmetries (mean + 2 S.D.) were set as 28.8 (500 Hz) and 52.3 (1000 Hz).

We also calculated 500–1000 VEMP slope. In healthy subjects, 500–1000 VEMP slope ranged from −16.6 to 30.0 [mean (S.D.) = 6.19 (12.9)] (Table 4). According to this result, the normal range of 500–1000 VEMP slope was set as −19.6~31.9.

The means (S.D.) of peak latencies are summarized in Table 5. According to this result, the upper limits of peak latencies were set (within mean + 2 S.D.) as shown in Table 5.

VEMPs in patients with MAV

For patients, 500-Hz and 1000-Hz TBs were applied. All patients with MAV had VEMP responses to 500-Hz TB, whereas all but one side of one patient showed responses to 1000-Hz TB (Table 6). The means and S.D.s of CA are shown in Table 7 and Fig. 3. Except for one patient, who showed absence of responses to 1000 Hz, interaural VEMP asymmetry was within normal limits.

In this group, the mean (S.D.) of 500–1000 slope of VEMP was 3.92 ± 27.2 (Table 4). Three sides of three patients (27% of patients) had significantly decreased 500–1000 VEMP slope, in other words, 1000 Hz dominant VEMP responses (Table 8, Fig. 4).

The peak latencies (mean + S.D.) were 14.3 ± 1.5 ms (p13 500 Hz), 21.4 ± 2.2 ms (n23 500 Hz), 13.3 ± 1.3 ms (p13 1000 Hz) and 20.9 ± 1.7 ms (n23 1000 Hz). Four sides of four patients showed significantly prolonged p13 latencies to 500-Hz TB (Tables 9 and 10). Of these four sides, two sides of two patients also had prolonged p13 latencies to 1000-Hz TB. None showed prolonged n23 latency. These four patients were different from three patients who showed 1000-Hz dominant VEMP responses.

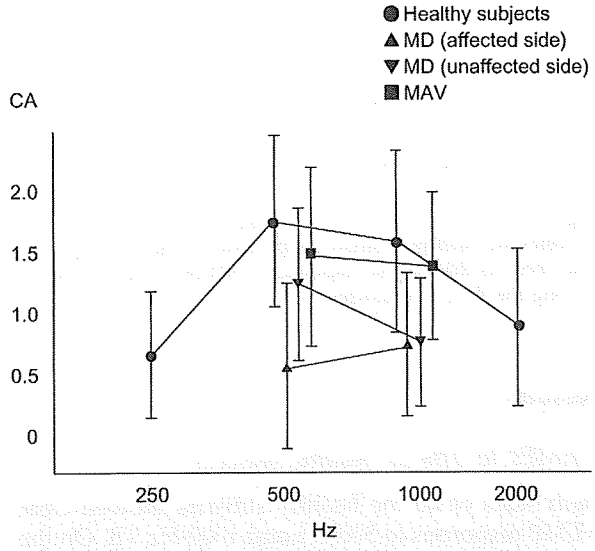

Figure 3 Corrected amplitudes in healthy subjects and patients with Meniere's disease (MD) and migraine-associated vertigo (MAV). Dots and bars represent means and standard deviations, respectively. See also Table 7.

VEMPs in patients with MD

Detection rates of VEMP responses are summarized in Table 6. Apart from absence of responses, two patients had significantly large interaural VEMP asymmetries suggesting decreased amplitudes on

Table 4 500–1000 vestibular-evoked myogenic potential slope

	n	Mean + S.D.	Median
Healthy subjects	16	6.19 + 12.9	7.93
MD (affected side)	9	−27.5 + 44.9	−20.5
MD (unaffected side)	11	31.8 + 41.6	16.2
MAV	22	3.92 + 27.2	−3.58
One-way ANOVA		$P = 0.0012$*	

*Bonferroni test indicated that significant difference was seen between the affected side and the unaffected side of MD patients ($P < 0.0001$).

MD, Meniere's disease; MAV, migraine-associated vertigo.

Table 3 Detection rates and corrected amplitudes (CAs) of vestibular-evoked myogenic potentials in healthy subjects

	250 Hz	500 Hz	1000 Hz	2000 Hz
Detection rate	68% (11/16)	100% (16/16)	100% (16/16)	87% (14/16)
Mean + S.D. of CA	0.65 + 0.49	1.76 + 0.69	1.60 + 0.74	0.91 + 0.64

Table 5 Peak latencies in healthy subjects (ms)

	p13 (500 Hz)	n23 (500 Hz)	p13 (1000 Hz)	n23 (1000 Hz)
Mean	13.7	22.0	13.1	20.6
S.D.	0.9	2.0	1.3	2.0
Upper limit of normal range (= mean + 2 S.D.)	15.5	26.0	15.7	24.6

Table 6 Detection rates of vestibular-evoked myogenic potentials in healthy subjects and patients

	500 Hz	1000 Hz
Healthy subjects	100% (16/16)	100% (16/16)
MD (affected side)	63% (7/11)	81% (9/11)
MD (unaffected side)	100% (11/11)	81% (9/11)
MAV	100% (22/22)	95% (21/22)
χ^2 test	$P = 0.0003$	$P = 0.19$

MD, Meniere's disease; MAV, migraine-associated vertigo.

Table 7 Mean + S.D. of corrected amplitudes in healthy subjects and patients

	500 Hz	1000 Hz
Healthy subjects	1.76 + 0.69	1.60 + 0.74
MD (affected side)	0.59 + 0.67	0.76 + 0.58
MD (unaffected side)	1.25 + 0.62	0.78 + 0.52
MAV	1.49 + 0.73	1.40 + 0.6
One-way ANOVA	$P = 0.0007$*	$P = 0.001$**

*Bonferroni test indicated that significant differences were seen between healthy subjects and the affected side of MD patients ($P < 0.0001$) and between MAV patients and the affected side of MD patients ($P = 0.001$).

**Bonferroni test indicated that significant differences were seen between healthy subjects and the affected side of MD patients ($P = 0.0012$) and between healthy subjects and the unaffected side of MD patients ($P = 0.0015$).

MD, Meniere's disease; MAV, migraine-associated vertigo.

Table 8 Incidence of significantly decreased 500–1000 vestibular-evoked myogenic potential slope

	For ears	For bodies
Healthy subjects	0% (0/16)	0% (0/8)
MAV	13% (3/22)	27% (3/11)
MD		45% (5/11)
(Affected side)	55% (5/9)	
(Unaffected side)	9% (1/11)	

MD, Meniere's disease; MAV, migraine-associated vertigo.

the affected side to 500-Hz TB. The means and S.D.s of CA are shown in Table 7 and Fig. 3.

In this group, the means (S.D.s) of 500–1000 VEMP slope were –27.5 ± 44.9 on the affected side and 31.8 ± 41.6 on the unaffected side. Concerning the affected side, five of the nine patients had significantly decreased 500–1000 VEMP slope, 1000 Hz dominant VEMP responses (Table 8, Fig. 5). On the unaffected side, one patient had a significant slope (Table 8).

The peak latencies (mean + S.D.) on the affected side were 13.9 ± 1.7 ms (p13 500 Hz), 21.5 ± 2.4 ms (n23 500 Hz), 13.5 ± 2.1 ms (p13 1000 Hz) and 21.3 ± 2.0 ms (n23 1000 Hz). One patient showed a prolonged 500-Hz TB and 1000-Hz TB (Tables 9 and 10).

Comparison of the groups

Detection rates of VEMP responses were significantly lower on the affected side of MD to 500-Hz TB ($P = 0.0003$, χ^2 test), while there was no significant differences concerning 1000-Hz TB ($P = 0.19$, χ^2 test) (Table 6).

Concerning 500–1000 VEMP slope, there were significant differences among the four groups ($P = 0.0012$, one-way ANOVA, Table 4). Bonferroni multiple comparison test indicated that 500–1000 VEMP slope of the affected side of MD was significantly smaller than that of the unaffected side ($P < 0.0001$).

Concerning CA, there were significant differences among the four groups ($P = 0.0007$ to 500-Hz TB and $P = 0.001$ to 1000-Hz TB, one-way ANOVA, Table 7). Bonferroni multiple comparison test indicated that CA to 500-Hz TB of the affected side of MD was significantly smaller than that of the healthy subjects ($P < 0.0001$) and that of the MAV patients ($P = 0.001$), and that CA to both 1000-Hz TB of the affected side and the unaffected side of MD were significantly smaller than that of the healthy

Table 9 Incidence of significantly prolonged peak latencies

	p13 (500 Hz)	n23 (500 Hz)	p13 (1000 Hz)	n23 (1000 Hz)
Healthy subjects	0% (0/16)	0% (0/16)	0% (0/16)	0% (0/16)
MAV	18% (4/22)	0% (0/22)	9% (2/22)	0% (0/22)
MD (affected side)	14% (1/7)	0% (0/7)	12% (1/8)	12% (1/8)
MD (unaffected side)	0% (0/11)	0% (0/11)	0% (0/8)	0% (0/8)

MD, Meniere's disease; MAV, migraine-associated vertigo.

Table 10 Peak latencies (mean + S.D.) (ms)

	p13 (500 Hz)	n23 (500 Hz)	p13 (1000 Hz)	n23 (1000 Hz)
Healthy subjects	13.7 + 0.9	22.0 + 2.0	13.1 + 1.3	20.6 + 2.0
MAV	14.3 + 1.5	21.4 + 2.2	13.3 + 1.2	20.9 + 1.7
MD (affected side)	13.9 + 1.7	21.5 + 2.4	13.5 + 2.1	21.3 + 2.0
MD (unaffected side)	14.2 + 0.94	22.8 + 2.0	13.3 + 2.0	21.6 + 1.5

MD, Meniere's disease; MAV, migraine-associated vertigo.

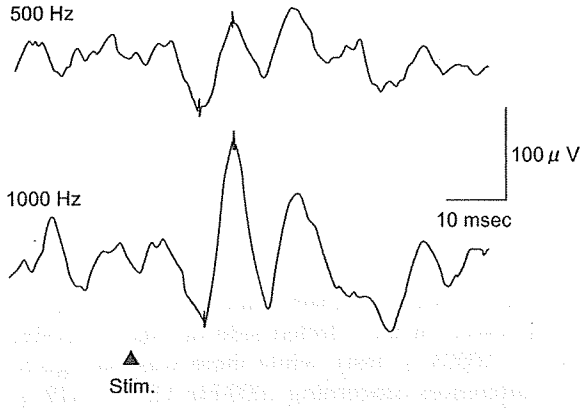

Figure 4 Vestibular-evoked myogenic potentials of a 48-year-old woman with migraine-associated vertigo (MAV) (responses on the left side). She showed significantly greater responses to 1000-Hz tone bursts (TB) than to 500-Hz TB (500–1000 slope = –23.8).

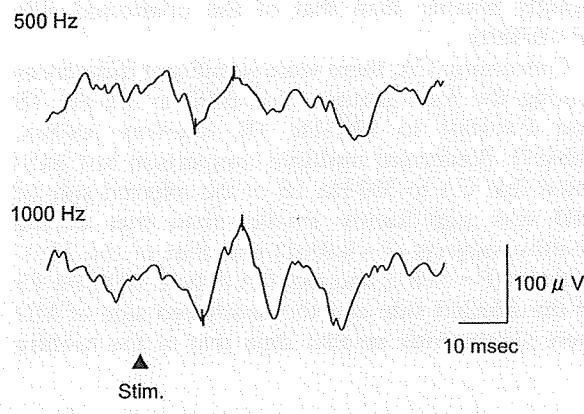

Figure 5 Vestibular-evoked myogenic potentials of a 70-year-old woman with left Meniere's disease (MD) (responses on the affected side). She showed significantly greater responses to 1000-Hz tone bursts (TB) than to 500-Hz TB (500–1000 slope = –20.5).

subjects ($P = 0.0012$ to the affected side and $P = 0.0015$ to the unaffected side). There was no significant differences of CA between healthy subjects and MAV patients.

There was no significant difference in the peak latencies among the four groups ($P > 0.05$, one-way ANOVA).

Discussion

Rauch et al. (18) reported that in healthy subjects, the largest amplitude and the lowest threshold of VEMP were obtained to 500-Hz TB, whereas patients with MD showed less tuning at 500 Hz and shifts of the best frequency to 1000 Hz. Rauch et al. attributed this shift to the change of resonant frequency in the saccule. Node et al. (29) showed the same tendency and also showed that this shift of the best frequency was normalized by furosemide administration, suggesting that this shift could be caused by endolymphatic hydrops. To quantify this tendency concerning frequency tuning, we adopted 500–1000 VEMP slope as a new parameter. Using this parameter, we confirmed that the affected side of MD patients shows a shift of VEMP response tuning to 1000 Hz (Table 4). We adopted this new parameter, 500–1000 VEMP slope, for MAV patients because we hypothesized that MAV and MD might share some common pathophysiological mechanisms. The comparison of the MAV group with healthy subjects did not show significant difference of 500–1000 VEMP slope. However, this result was unsurprising, because MAV may be heterogeneous. In other words, perhaps, MAV has diverse aetiologies (12). The fact that the rate of significantly decreased 500–1000 VEMP slope, indicating the shift of VEMP response tuning to 1000 Hz in MAV patients, was relatively high (3/11, 27%) (Table 8) supports our hypothesis that MAV and MD might share some common pathophysiological mechanisms.

What are the common pathophysiological mechanisms between MAV and MD? Node et al. showed that this shift of the best frequency was normalized by furosemide administration (29), suggesting that the shift could be caused by endolymphatic hydrops. Therefore, the shared common condition

could be endolymphatic hydrops. Ishiyama et al. (30) have reported that patients with MAV could have vestibular drop attack, Tumarkin's otolithic crisis, or sudden fall without loss of consciousness, which is usually seen in patients with MD (31–33).

How does migraine cause endolymphatic hydrops? Dieterich et al. (34) and Iwasaki et al. (10) reported that patients with MAV had canal paresis on the caloric test, which implies peripheral vestibular dysfunction. Patients with MAV could have inner ear damage. Trigeminal nerve endings have been found in the vessels in the inner ear (35). Neurogenic inflammation could cause change of the blood flow in the inner ear, which might lead to change of the inner ear condition. Furthermore, expression of transient receptor potential channel vanilloid subfamily1 (TRPV1), which is a nociceptive receptor associated with migraine, has been found in the human endolymphatic sac (36). Therefore, migraine might affect the absorption of the endolymph in the endolymphatic sac, resulting in endolymphatic hydrops.

Concerning VEMPs in patients with migraine or MAV, Allena et al. and Roceanu et al. have shown decreased amplitudes of VEMP in patients with migraine (21, 22). Although our study did not confirm this tendency, it might be due to the difference of stimulation (tone bursts vs. click) or the smallness of the size of our study.

Finally, we would like to point out another interesting finding in this study. We found that significantly prolonged p13 latencies were observed in four ears of four patients (4/11, 36%). The four patients with prolonged p13 were different from the three patients with significantly decreased 500–1000 VEMP slope. Prolonged peak latencies suggest retro-labyrinthine lesions, including brainstem lesions (26). Therefore, the four patients with prolonged latencies might have vestibular nerve lesions or brainstem lesions, whereas the three patients with frequency shift might have labyrinthine lesions. Different types of abnormal findings on VEMP in patients with MAV might reflect differences in aetiology. In other words, VEMP might contribute to classification of MAV by difference of aetiology.

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CASE REPORT

Vestibular schwannoma with absent vestibular evoked myogenic potentials to clicks but normal ABR, caloric responses and vestibular evoked myogenic potentials to 500 Hz tone bursts

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Abstract

We report a case of vestibular schwannoma with absent vestibular evoked myogenic potentials (VEMPs) to clicks but normal auditory brainstem responses, caloric responses, and vestibular evoked myogenic potentials to 500 Hz tone bursts. This patient visited our clinic with complaint of sudden right hearing loss. This was the third episode of hearing loss in his right ear. Due to atypical medical history, he underwent further neuro-otological and neuroradiological examinations. Among the neurophysiological tests, only VEMPs to clicks showed abnormal findings (absent responses on the right). MRI revealed a small vestibular schwannoma in the right internal auditory meatus, which was considered to be of inferior vestibular nerve origin. This case suggested that VEMPs to clicks should still be included in the test batteries for the diagnosis of vestibular schwannoma.

Keywords: *Acoustic neuroma, vestibular schwannoma, VEMP, ABR, inferior vestibular nerve*

Introduction

Vestibular schwannoma (VS) usually arises from the vestibular division of the eighth cranial nerve (vestibular nerve) [1]. When patients have persistent cochlear and/or vestibular symptoms not fully explained by another cause, VS should be considered [2]. At this stage, neuro-otological and audiological tests and neuro-imaging studies are required. As neuro-otological and audiological tests, pure-tone audiometry, ABR (auditory brainstem response), VEMP (vestibular evoked myogenic potential), and caloric test are often performed [2,3]. Pure-tone audiometry is a screening test for hearing loss. ABR, VEMP, and caloric test are representative neurophysiological tests of the cochlear nerve, the inferior vestibular nerve, and the superior vestibular nerve, respectively [2]. MRI (magnetic resonance imaging) is recommended as a neuro-imaging study. The sensitivity of VEMP and the caloric test is approximately 80% in patients with VS, while the sensitivity of ABR is >95% [3,4]. Although ABR seems superior to VEMP and the caloric test from the viewpoint of sensitivity, some patients have normal ABR but abnormal VEMP [5]. Furthermore, ABR is not applicable to patients with profound hearing loss. Therefore, VEMP could be included as a choice for test batteries [2]. VEMP also attracts clinicians' attention from the viewpoint of the detection of nerve origin of VS. Herein, we report a patient with a small VS that presented with absent VEMPs to clicks but normal ABR, caloric responses and VEMPs to 500 Hz tone bursts.

Case report

A 24-year-old otherwise healthy man presented with complaint of acute onset hearing loss in the right ear. He told us that it was the third experience of

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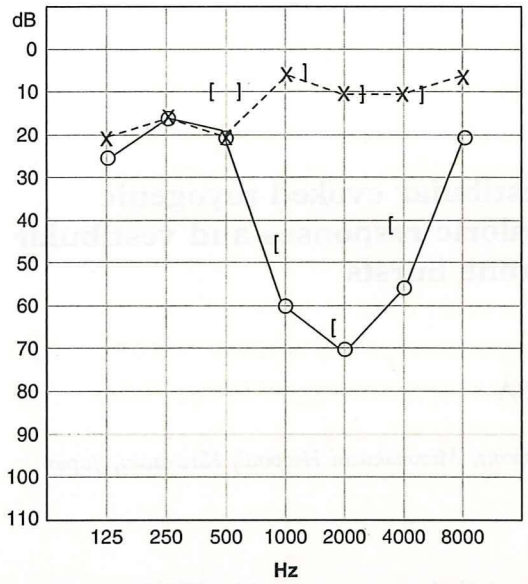

Figure 1. Pure tone hearing at the first visit. O, hearing level to right air-conducted sound; X, hearing level to left air-conducted sound; [, hearing level to right bone-conducted sound;], hearing level to left bone-conducted sound.

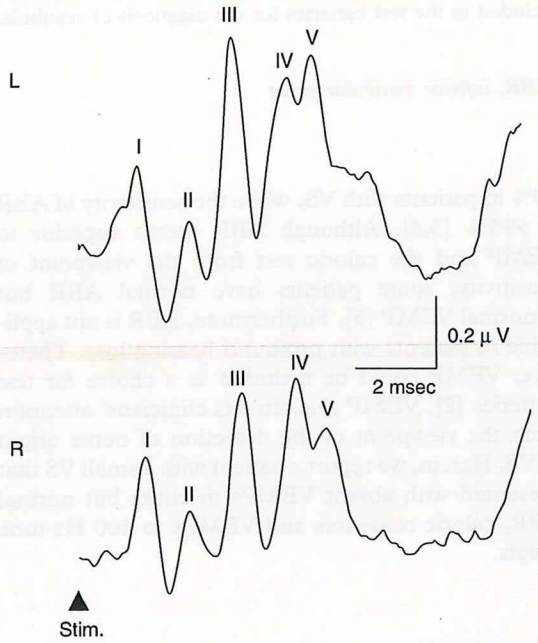

Figure 2. ABR to 80 dBnHL clicks.

right acute hearing loss and that he had recovered from the first and second episodes of hearing loss. He did not have vertigo or dizziness. On examination, he showed trough-shaped sensorineural hearing loss on the right (Fig. 1). He did not

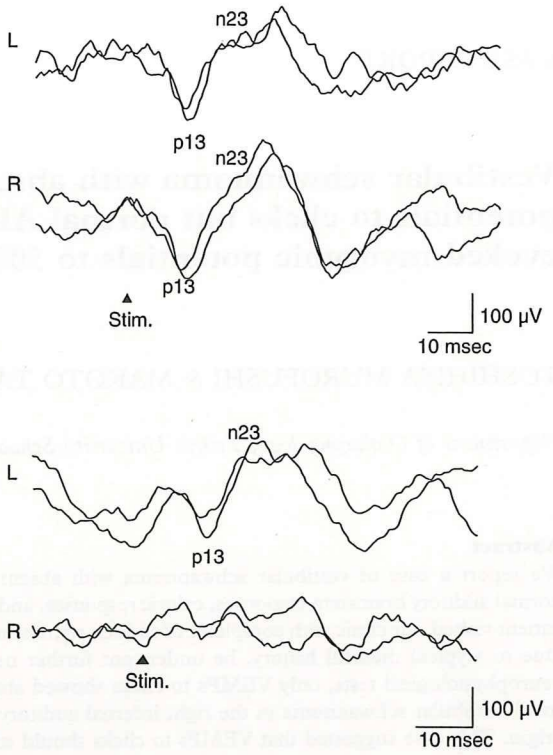

Figure 3. VEMPs: (a) to 95 dBnHL 500 Hz tone bursts; (b) to 95 dBnHL clicks.

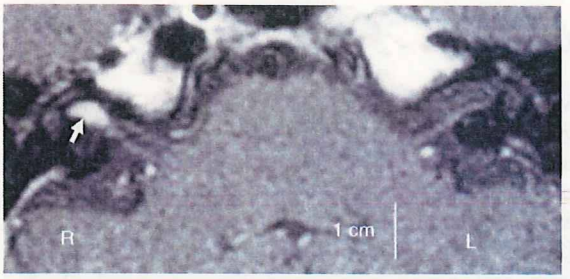

Figure 4. T1-weighted axial MRI enhanced by Gd-DTPA. There is a high intensity mass (white arrow, 6 mm in diameter) in the right internal meatus.

show gaze-evoked or positional nystagmus. The Fukuda (Unterberger) stepping test was normal. He underwent steroid therapy (tapered from 500 mg/day of hydrocortisone sodium succinate), having improvement of hearing (61 dBHL pretreatment to 36 dBHL post-treatment at the average hearing level of 1000, 2000, and 4000 Hz). However, since his medical history was atypical for idiopathic sudden sensorineural hearing loss, we recommended that he should undergo further neurophysiological and neuroradiological studies.

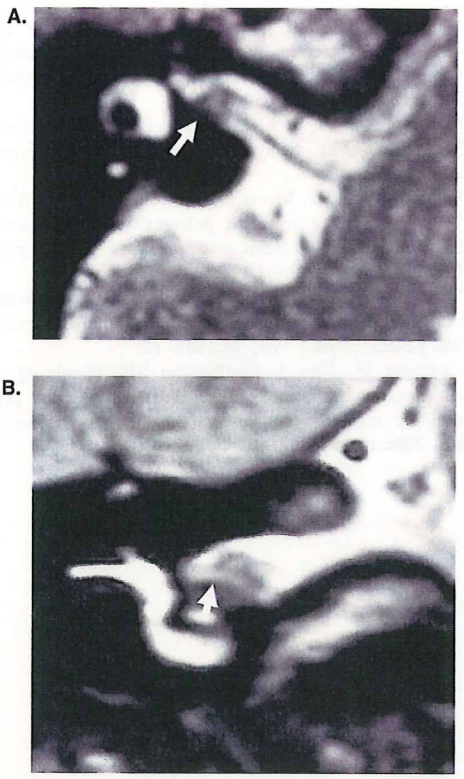

Figure 5. T2-weighted MRI without contrast medium. White arrows indicate the tumor. (a) Axial view; (b) coronal view.

ABR to 80 dBnHL clicks was normal on both sides (Fig. 2). Caloric test to cold water showed 16% canal paresis (CP) on the right, which is a normal response [3]. His VEMPs to 500 Hz tone bursts (95 dBnHL) were normal on both sides, but VEMPs to clicks (95 dBnHL) were absent on the right (Fig. 3). MRI revealed a small tumor (6 mm) that was enhanced by Gd-DTPA (Fig. 4). Because the tumor was in the caudo-ventral part of the internal auditory meatus (Fig. 5), it was considered of inferior vestibular nerve origin. This patient is currently under observation with regular MRI scanning.

Discussion

As regards the relationship of the nerve origin of VS to neurophysiological test results, previous studies have shown negative results [3,6,7]. According to the study by Ushio et al. [3], the rate of abnormal responses on caloric test and VEMPs was not different between patients with superior VS and those with inferior VS. They assumed that the tumor could extend outwardly and result in dysfunction of nerves other than those involved in the origin of the tumor. Their assumption may be right. However, when the tumor is very small, it is expected that a patient may show abnormal results only on those tests that examine the function of the original nerve. The patient in this study may be such a case.

Concerning this case, two questions remain. The first question is the cause of acute hearing loss in this patent. As he had three episodes of acute hearing loss, his acute hearing loss should be attributed to the existence of the VS. According to the study by Gouveris et al. [8], distortion products of otoacoustic emission (DPOAEs) begin to decrease even at the early stages of hearing loss. Perhaps, disturbances of the blood supply in the internal auditory meatus might cause cochlear dysfunction (not cochlear nerve) resulting in acute hearing loss, although our patient did not undergo DPOAE testing. Haemorrhage from a tumor might be another possible cause of acute hearing loss.

The second question is the reason for the discrepancy in results between VEMPs to clicks and VEMPs to 500 Hz tone bursts. According to Patko et al. [9] click is more sensitive than 500 Hz tone bursts for detection of abnormalities in patients with VS. Among the 134 VS patients who showed abnormal VEMPs to clicks, 32 patients showed normal responses to 500 Hz tone bursts. They assumed that clicks might be useful for the detection of minor saccular dysfunction, while 500 Hz tone bursts could provide information concerning potential residual functions of the saccule. Their assumption is probably right, because it was reported that the best frequencies for saccular afferents in cats are between 500 Hz and 1000 Hz [10]. However, as another possible explanation, one might assume that the utricle might respond to 500 Hz tone bursts, because recently it has been known that utricular afferents in guinea pigs could respond to bone-conducted vibration [11]. Further study is needed to clarify this point.

In conclusion, VEMPs to clicks should still be included in test batteries for the diagnosis of VS.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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