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Eliciting Constant and Prominent Waves n34–p44 of Vestibular-evoked Myogenic Potentials

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Objective—The serial peaks of vestibular-evoked myogenic potentials (VEMPs) have been labeled p13, n23, n34 and p44 according to their latency. Waves p13–n23 have been shown to be of saccular origin, whereas the origin of waves n34–p44 is still unknown. In order to improve the clinical applicability of waves n34–p44, we examine the use of different patterns of acoustic stimuli to evoke constant and prominent VEMPs, especially waves n34–p44.

Material and Methods—In this prospective study 27 healthy volunteers (54 ears) underwent VEMP tests. Three kinds of click intensity (85, 95 and 105 dB nHL) were presented in a random order to evoke 85-VEMP, 95-VEMP and 105-VEMP, respectively. The response rate, latency of each peak, peak-to-peak interval and amplitude of waves p13–n23 and n34–p44 were measured and analyzed.

Results—The response rates of waves p13–n23 in 85-VEMP, 95-VEMP and 105-VEMP were 26% (14/54), 89% (48/54) and 98% (53/54), respectively. Significant differences in the response rate existed between 85-VEMP and both 95-VEMP and 105-VEMP ($p < 0.01$), whereas there was a non-significant difference between 95-VEMP and 105-VEMP ($p > 0.05$). In contrast, the response rates for eliciting waves n34–p44 were 19% (10/54), 63% (34/54) and 89% (48/54), using 85, 95 and 105 dB acoustic stimuli, respectively. A significantly higher response rate for waves n34–p44 occurred when the intensity of the stimuli increased ($p < 0.01$). Although neither latencies nor interval exhibited a significant difference between 95-VEMP and 105-VEMP, the amplitude of 105-VEMP was significantly greater than that of 95-VEMP for both waves p13–n23 and n34–p44.

Conclusion—An acoustic stimulus intensity of 105 dB nHL is required to reliably elicit waves n34–p44 in subjects with normal hearing. *Key words: click, intensity, vestibular-evoked myogenic potential, wave n34–p44, wave p13–n23*.

INTRODUCTION

Colebatch et al. (1) successfully applied loud sounds to evoke vestibular-evoked myogenic potentials (VEMPs) in the tonically contracted ipsilateral sternocleidomastoid (SCM) muscle, and labeled the serial peaks p13, n23, n34 and p44, based on their latencies. In contrast to the biphasic waves p13–n23, which are supposed to originate from the sacculo-collic reflex (2–5), the origin of waves n34–p44 remains undetermined, although a cochlear origin has been proposed because waves n34–p44 could be obtained in ears after selective vestibular nerve section (1). In the past decade, VEMPs have been widely studied in several clinical diseases, such as Ménière's disease (6), cerebellopontine angle tumor (7), multiple sclerosis (8), superior canal dehiscence syndrome (9), etc. However, researchers have focused almost solely on investigating waves p13–n23, possibly due to the higher response rate in normal controls. In contrast, waves n34–p44 could be elicited in only 55–60% of healthy subjects, interrupting the investigation of their clinical significance (1, 10). The aim of this study was therefore to elicit steady and prominent waves n34–p44 with a higher response rate in normal subjects in order to improve their clinical applicability.

MATERIAL AND METHODS

Twenty-seven healthy volunteers (15 males, 12 females; mean age 32 years; range 21–40 years) underwent VEMP tests. All subjects denied any previous ear diseases. Surface electromyographic (EMG) activity was recorded (Medelec Synergy, Old Woking, UK) in a supine subject, with an active electrode placed on the upper half of the SCM muscle and a reference electrode placed on the lateral end of the upper sternum. During the recording, the subject was instructed to hold his/her head slightly raised in order to activate the SCM muscles. EMG activities were monitored on a display so as to maintain them at a constant level (50–200 μV) in individual test ears. EMG signals were amplified and band-filtered between 20 and 2000 Hz. Three kinds of click intensity (85, 95 and 105 dB nHL) were given through a headphone to elicit 85-VEMP, 95-VEMP and 105-VEMP, respectively. The stimulation rate was 5 Hz and the analysis time for each stimulus was 50 ms. In total, 128 consecutive trials to stimuli were averaged for each run. Two reproducible runs were averaged as the final response.

The initial positive/negative polarity of the waveform with peaks termed p13 and n23 based on their

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latencies was used to determine the presence or absence of waves p13–n23. The subsequent negative/positive polarity of the waveform was defined as peaks n34 and p44 according to their latencies. The relative amplitude indicated the amplitude of 95-VEMP divided by that of 105-VEMP in either waves p13–n23 or n34–p44 for the same test ear. The response rate, latency of each peak, peak-to-peak interval and amplitude of waves p13–n23 and n34–p44 were measured and analyzed. Comparative analysis of these results was conducted using McNemar's test, a two-tailed paired t-test and the Wilcoxon signed-rank test (11). $p < 0.05$ was considered significant. This study was approved by the institutional review board and each subject gave their informed consent to participate.

RESULTS

Waves p13–n23

All 27 normal volunteers (54 ears) completed VEMP tests using various click stimuli. The response rates for eliciting waves p13–n23 using 85, 95 and 105 dB acoustic stimuli were 26% (14/54), 89% (48/54) and 98% (53/54), respectively. Significant differences in the response rate existed between 85-VEMP and both 95-VEMP and 105-VEMP ($p < 0.01$; McNemar's test), whereas there was a non-significant difference between 95-VEMP and 105-VEMP ($p > 0.05$; McNemar's test; Fig. 1A). Excluding six ears with absent waves p13–n23 in 95-VEMP, a total of 48 ears were compared. The mean latencies of waves p13 and n23 and the peak-to-peak interval of 95-VEMP were 11.91 ± 0.94, 19.09 ± 1.38 and 7.18 ± 1.54 ms, respectively, whereas those of 105-VEMP were 11.90 ± 0.93, 19.12 ± 1.41 and 7.21 ± 1.21 ms, respectively. There was a non-significant difference between 95-VEMP and 105-VEMP for all of these parameters ($p > 0.05$; two-tailed paired t-test; Table I). The minimum, maximum and median amplitudes of waves p13–n23 in 95-VEMP were 44.20, 240.65 and 93.90 μV, respectively, and the corresponding values for 105-VEMP were 43.35, 297.9 and 122.50 μV. The minimum, maximum and median relative amplitudes were 44%, 130% and 84%, respectively (Table II). Since the tonic EMG activities were maintained at a constant level only in individual ear recordings, Wilcoxon signed-ranks in amplitudes p13–n23 of 105-VEMP − 95-VEMP on the same testing ears, rather than the absolute amplitudes, were used for analysis. Hence, the amplitude p13–n23 of 105-VEMP was significantly larger than that of 95-VEMP ($p < 0.01$; Wilcoxon signed-rank test).

Waves n34–p44

The response rates for eliciting waves n34–p44 were 19% (10/54), 63% (34/54) and 89% (48/54) using 85, 95 and 105 dB acoustic stimuli, respectively. A significantly higher response rate for waves n34–p44 occurred when the intensity of the stimuli increased ($p < 0.01$; McNemar's test; Fig. 1B). After excluding 20 ears with absent waves n34–p44 in either 95-VEMP or 105-VEMP, the remaining 34 ears were compared and analyzed. The mean latencies of waves n34 and p44 and the peak-to-peak interval of 95-VEMP were 29.98 ± 2.28, 37.64 ± 2.87 and 7.66 ± 1.79 ms, respectively, whereas those of 105-VEMP were 30.16 ± 2.43, 37.56 ± 2.95 and 7.40 ± 1.64 ms, respectively; these

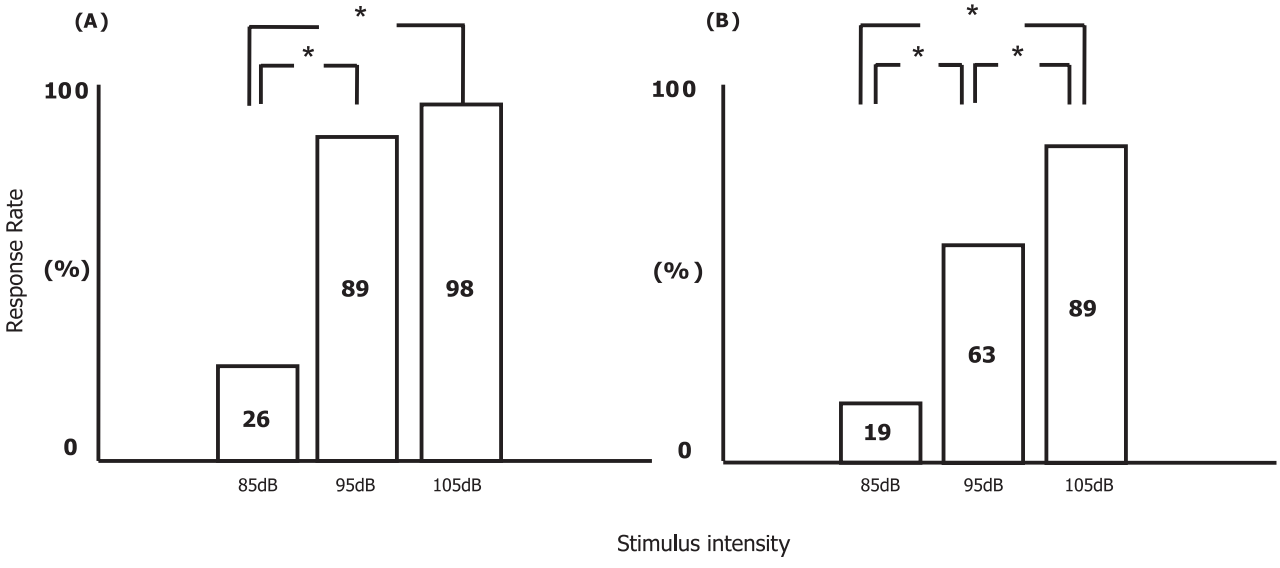

Fig. 1. Comparison of response rates of VEMPs using varied acoustic stimuli: (A) waves p13–n23; (B) waves n34–p44. Asterisk indicates $p < 0.01$.

Table I. *Latencies and interval of waves p13–n23 in 95-VEMP and 105-VEMP. Results are expressed as mean ± SD*

	No. of ears	Latency p13 (ms)	Latency n23 (ms)	Interval p13–n23 (ms)
95-VEMP	48	11.91 ± 0.94	19.09 ± 1.38	7.18 ± 1.54
105-VEMP	48	11.90 ± 0.93	19.12 ± 1.41	7.21 ± 1.21
p		NS	NS	NS

Table II. *Amplitude and relative amplitude of waves p13–n23 elicited using various click stimuli*

	No. of ears	Minimum	Maximum	Median	IQR
Amplitude p13–n23 (μV)					
95-VEMP	48	44.20	240.65	93.90	51.46
105-VEMP	48	43.35	297.90	122.50	71.46
Relative amplitude (%)	48	44	130	84	27

IQR = inter-quartile range.

differences were not significant ($p > 0.05$; two-tailed paired *t*-test; Table III). The minimum, maximum and median amplitudes of waves n34–p44 in 95-VEMP were 21.30, 178.45 and 62.35 μV, respectively, and the corresponding values for 105-VEMP were 26.10, 186.09 and 62.95 μV. The minimum, maximum and median relative amplitudes were 41%, 159% and 95%, respectively (Table IV). The amplitude n34–p44 of 105-VEMP was significantly greater than that of 95-VEMP ($p = 0.03$; Wilcoxon signed-rank test).

Waves p13–n23 versus waves n34–p44

For comparing waves p13–n23 and n34–p44, a total of 34 ears that presented both waves were statistically analyzed. The peak-to-peak intervals of waves p13–n23 and n34–p44 were 7.18 ± 1.52 and 7.66 ± 1.79 ms, respectively in 95-VEMP, compared to 7.24 ± 1.50 and 7.40 ± 1.64 ms, respectively in 105-VEMP; the differences between waves p13–n23 and n34–p44 in either 95-VEMP or 105-VEMP were not significant ($p > 0.05$; two-tailed paired *t*-test). The amplitude of waves p13–n23 was significantly greater than that of waves n34–p44 in either 95-VEMP or 105-VEMP ($p < 0.01$; Wilcoxon signed-rank test; Table V).

DISCUSSION

The definite origin of waves n34–p44 is still unknown. On the one hand, as waves n34–p44 could be obtained in ears after selective vestibular nerve section, it was proposed that they probably arose from cochlear afferents (1). On the other hand, waves n34–p44 could also be obtained in deaf ears (10), implying that they were probably not of cochlear origin only. Taking these results together suggests that waves n34–p44 may have both a cochlear and vestibular origin. One possible pathway to explain this dual origin, in addition to the cochlear afferent, is the vestibulo-cochlear projection, which has been proven to arise from saccular afferents to the cochlear nucleus in guinea pigs (12, 13). Another question is whether waves n34–p44 are related to the startle reflex. The acoustic startle reflex is a relatively simple motor response characterized by rapid habituation and a latency of ≈ 50 ms, in contrast to the higher rates of repetition and shorter latency (Table III) of waves n34–p44 (14). Consequently, the startle reflex would not seem to be involved in waves n34–p44. Further electrophysiological or pathological study is necessary

Table III. *Latencies and interval of waves n34–p44 in 95-VEMP and 105-VEMP. Results are expressed as mean ± SD*

	No. of ears	Latency n34 (ms)	Latency p44 (ms)	Interval n34–p44 (ms)
95-VEMP	34	29.98 ± 2.28	37.64 ± 2.87	7.66 ± 1.79
105-VEMP	34	30.16 ± 2.43	37.56 ± 2.95	7.40 ± 1.64
p		NS	NS	NS

Table IV. *Amplitude and relative amplitude of waves n34–p44 elicited using various click stimuli*

	No. of ears	Minimum	Maximum	Median	IQR
Amplitude n34–p44 (μV)					
95-VEMP	34	21.30	178.45	62.35	39.60
105-VEMP	34	26.10	186.09	62.95	42.72
Relative amplitude (%)	34	41	159	95	28

IQR = inter-quartile range.

to elucidate the mechanism of waves n34–p44, so that they can be applied to study labyrinthine or retrolabyrinthine disorders in the future.

In order to evoke constant and prominent VEMPs, many researchers have attempted to establish the optimum stimulus for VEMPs. In our laboratory, the ideal stimulus pattern for evoking waves p13–n23 by short tone bursts (STBs) is as follows: frequency 500 Hz; stimulation repetition rate 5 Hz; rise/fall time 1 ms; plateau time 2 ms (15–17). However, the ideal stimulus intensity for eliciting waves p13–n23 and n34–p44 remains undetermined. Because clicks seem better than STBs for evoking marked VEMPs with a higher response rate in healthy subjects (18), we used clicks instead of STBs as acoustic stimuli in this study.

When the stimulus intensity was incremented, the response rate of waves p13–n23 increased from 26% in 85-VEMP to 89% in 95-VEMP, and this difference was significant ($p < 0.01$). However, no statistical difference in response rate was noted between 95-VEMP (89%) and 105-VEMP (98%), indicating that 95 dB is the minimum acoustic stimulus level to yield constant waves p13–n23. In contrast to waves p13–n23, the response rate of waves n34–p44 was increased significantly from 63% in 95-VEMP to 89% in 105-VEMP, meaning that 105 dB acoustic stimuli are required for eliciting constant waves n34–p44 (Fig. 2).

In both biphasic waves p13–n23 and n34–p44, neither latencies nor interval exhibited a significant difference between 95-VEMP and 105-VEMP (Tables I and III), which differed from the result of a previous report (19) that a lower stimulus intensity evoked responses with a statistically shorter latency of waves p13–n23. Although a decreasing wave latency following an increasing stimulus intensity was demonstrated in auditory brainstem responses (ABRs) (20), it was not observed in VEMPs in our study. One possible explanation for this observation is the difference between ABRs (neurogenic potentials) and VEMPs (myogenic potentials). Furthermore, both waves p13–n23 and n34–p44 were recorded from the same muscle, which may explain why no significant difference in peak-to-peak interval was exhibited between them in either 95-VEMP or 105-VEMP.

In terms of amplitude, we kept the tonic EMG activity at a constant level (50–200 μV) by means of EMG monitoring during VEMP recording and the testing sequence of acoustic intensity was performed in a random order in order to exclude the linear effect of tonic EMG activity on VEMP amplitude (21). Our data disclosed that both amplitudes p13–n23 and n34–p44 in 95-VEMP decreased significantly compared to those in 105-VEMP. However, the effect of stimulus intensity was more significant on the amplitude of waves p13–n23 than on that of waves n34–p44, as a 16% reduction was seen in the relative amplitude of waves p13–n23, compared to only a 5% reduction in that of waves n34–p44 (Tables II and IV).

Compared to waves p13–n23, not only the longer latency but also the smaller amplitude of waves n34–p44 indicated that different neural pathways were involved. Waves p13–n23 of VEMPs represent the

Table V. *Amplitude of waves p13–n23 and n34–p44 in 95-VEMP and 105-VEMP*

Amplitude (μV)	No. of ears	Minimum	Maximum	Median	IQR
95-VEMP					
Waves p13–n23	34	44.20	240.65	93.90	47.82
Waves n34–p44	34	21.30	178.45	62.35	39.60
105-VEMP					
Waves p13–n23	34	43.35	297.70	122.50	63.69
Waves n34–p44	34	26.10	186.09	62.95	42.72

IQR = inter-quartile range.

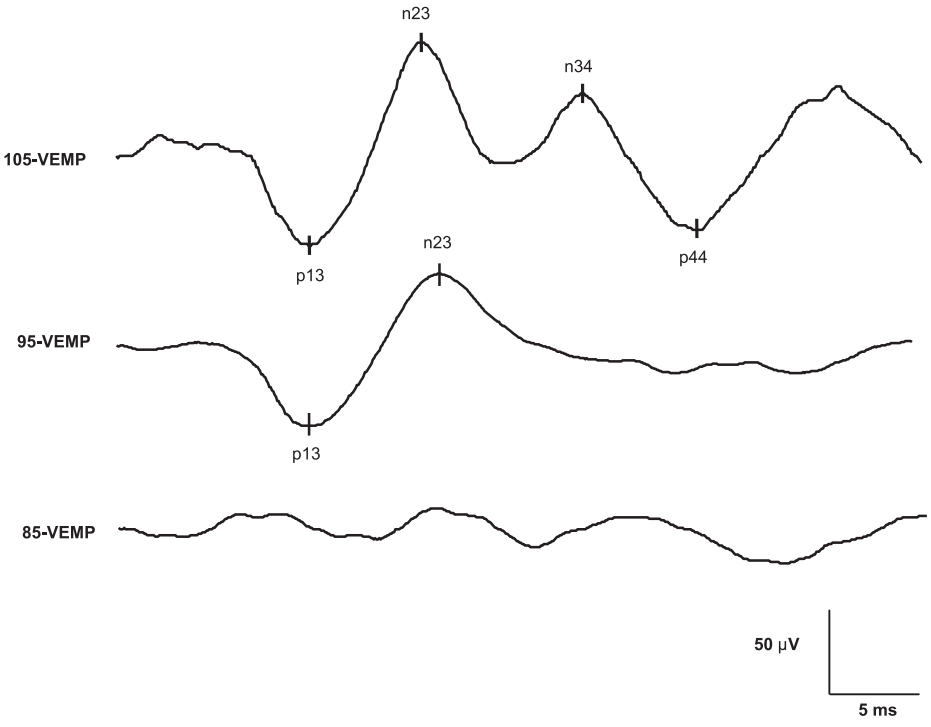

Fig. 2. VEMPs elicited in the right ear of a 30-year-old woman. Waves p13–n23 were observed for both 95-VEMP and 105-VEMP, compared to waves n34–p44 only for 105-VEMP. No waveform was identified in 85-VEMP.

sacculo-collic reflex, which is generated via a disynaptic pathway beginning in the saccular macula and then runs via the inferior vestibular nerve, lateral vestibular nucleus and medial vestibulospinal tract, before finally terminating in the motor neurons of the SCM muscle (1, 3, 5, 22, 23); i.e. vestibulocollic neurons are monosynaptically excited from the ipsilateral saccule and terminate on neck motoneurons. In contrast, the latency of waves n34–p44 was much longer than that of waves p13–n23 but they had similar peak-to-peak intervals, implying that the former might occur via a polysynaptic pathway, also terminating on the motor neuron of SCM muscles. As monosynaptic effects of vestibulospinal fibers, both excitatory and inhibitory, are most powerful in neck motoneurons (24), it would be anticipated that the amplitude of p13–n23 would be larger than that of n34–p44 (Table V).

In conclusion, the clinical application of waves n34–p44 is limited due to their lower response rate compared to that of waves p13–n23 in healthy subjects. Based on this study, we recommend that 105 dB nHL acoustic stimuli are required to reliably elicit waves n34–p44 in subjects with normal hearing.

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