Seasickness Pathogenesis and the Otolithic Organs: Vestibular Evoked Myogenic Potentials Study – Preliminary Results

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Abstract

Background: Seasickness is thought to result from conflicting inputs from the vestibular, visual and somatosensory systems. The otolithic organs, which are responsible for the sensation of linear acceleration and tilt, are important in the pathogenesis of seasickness. The vestibular evoked myogenic potentials test is an objective evaluation of saccular function.

Objective: To examine whether saccular function is related to the pathogenesis of seasickness.

Methods: VEMP was performed in 10 subjects susceptible to seasickness and in 14 non-susceptible subjects.

Results: Bilateral VEMP responses were obtained in 7 (50%) of the non-susceptible subjects and 1 (10%) of the susceptible subjects. No differences were found between the groups in P13 and N23 wave latencies, amplitudes, N13-P23 inter-peak latencies, and peak-to-peak asymmetry ratios. More subjects in the susceptible group had asymmetry ratios > 35%.

Conclusions: The attenuated saccular response might be explained in the context of the neural-mismatch theory and/or the subjective vertical theory, as reflecting an adaptation effort to sea conditions. A larger study is necessary to determine whether a statistically significant difference in VEMP responses exists between seasickness-susceptible and non-susceptible subjects.

Motion sickness is an expression of a physiological response to unfamiliar motion patterns, whether real or apparent. Seasickness is one of the most prevalent forms of motion sickness, but only one of many non-terrestrial motion patterns can provoke this response. Its main signs and symptoms include epigastric awareness, pallor, cold sweating, and nausea that progresses in severe cases to recurrent vomiting. Other frequently encountered manifestations include headache, drowsiness, sleepiness, apathy, depression, and a reduction in cognitive function reflected by reduced performance on various psychomotor tasks [1]. Our current understanding views motion sickness as arising from and signaling conflicting information processed within a multimodal sensory system whose function is to determine the individual’s motion relative to his or her environment. This has been termed the “neural mismatch and sensory rearrangement theory” [2]. According to this theory, inputs from the vestibular system (semicircular canals and otolithic organs), visual and somatosensory systems converge on the vestibular nuclei, cerebellum and parietal cortex, and are integrated into a common signal. In addition, these investigators [1,2] postulate the existence of a “neural store” for motion cue expectations based on past experience. A conflict occurs when the integrated sensory signal is compared and found at variance with the stored motion patterns. This results in the generation of a “mismatch signal” that initiates the cascade of events leading to motion sickness. At the same time, postural control adapts to different environments by integrating visual, vestibular and somatosensory inputs and changing the influence of each to meet the circumstances and decrease the mismatch.

A recent theory proposed by Bos and Bles and teams [3,4] suggests that uncertainty in the perception of vertical orientation is the specific cause of motion sickness. According to the subjective vertical conflict theory, all situations provoking motion sickness are characterized by a condition in which the sensed vertical is at variance with the subjective vertical that is expected from previous motion experience [5]. This theory points to the importance of the otolithic organs, which are responsible for the sensation of linear acceleration and tilt, in the pathogenesis of motion sickness. In support of this theory, bilateral utriculosacculectomy in the squirrel monkey rendered the animals refractory to motion-induced emesis [6]. Also, astronauts who reported motion sickness during Coriolis stimulation on earth were almost immune under microgravity conditions where otolithic stimulation is minimized [7]. These findings can also be explained in the theoretical context of sensory conflicts: Ablation of the otolithic maculae or complete temporary lack of otolithic stimuli would abort any sensory conflict that involves the otolithic inputs and would diminish the sensitivity to motion sickness.

During the last decade, an objective test of saccular function was developed. Click-evoked myogenic potentials of the tonically activated sternocleidomastoid muscle were first reported by Colebatch and Halmagyi [8], who observed that this response disappeared after vestibular nerve section despite preservation of hearing. These ipsilateral biphasic responses are preferably evoked by brief loud clicks [9] and can be detected by surface electrodes placed over the SCM ipsilateral to the stimulated ear.

VEMP = vestibular evoked myogenic potentials
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SCM = sternocleidomastoid muscle
These potentials are referred to as vestibular evoked myogenic potentials and result from activation of neural pathways descending from the vestibular nuclei via the medial vestibulospinal tract to the SCM motor nucleus. Several studies have demonstrated that the VEMP originates from saccular afferents [10,11]. While the saccule functions as the principal organ of hearing in some lower vertebrates [12], it has retained acoustic sensitivity in mammals [8]. This acoustic sensitivity of the saccule has been attributed to its proximity to the footplate of the stapes, which leads to its mechanical stimulation in response to sound.

The objective of the present study was to examine whether seasickness susceptibility is related to saccular function. The specific hypothesis was that differences in VEMP responses, which are related to the ability to sense linear acceleration and head tilt, would also reflect differences in the susceptibility to seasickness.

Patients and Methods

Ten seasickness-susceptible and 14 non-seasickness-susceptible healthy male Israeli naval crew members aged 19–24 years participated in the study. The seafaring experience of the susceptible group was at least 6 months in order to allow for adaptation to sea conditions. The subjects did not have any vestibular, musculoskeletal or neurological signs or symptoms, and all had normal findings on otoneurological examination. Normal hearing and lack of any air-bone gaps were established by pure-tone and speech audiometry. None of the subjects had taken medications for at least 72 hours before testing, and none consumed drugs or alcohol.

Seasickness symptoms and signs were self-reported by the study participants and then scored using the questionnaire of Wiker et al. [13]. For the purpose of the present study, susceptible subjects were selected from among those scoring 7 on the Wiker scale (the highest degree of susceptibility denoting frank vomiting in most sea conditions), while non-susceptible subjects were selected from among those scoring up to 4 on the Wiker scale.

All the VEMP tests were performed by one of the authors (P.G.), who was blinded to the subject’s degree of seasickness susceptibility. VEMP was performed using the Bio-logic system (Bio-logic Systems Corp., Mundelein, IL, USA).

Surface electromyographic activity was recorded in the sitting position from symmetric sites over the main bulk of the SCM muscle at a point approximately half the distance between the mastoid tip and the external auditory meatus. A reference electrode was placed on the side of the upper sternum. A ground electrode was placed on the forehead. During the recording, the subjects were instructed to press their chins against a chin-rest, taken from a standard ophthalmologic slit-lamp to activate the SCM. The electromyographic signal from the stimulated side was amplified and bandpass filtered (30–2000 Hz). Rarefaction clicks at 90 dB HL were presented through insert earphones to the ear being examined. The stimulation rate was 5.2 Hz, and the analysis time was 50 milliseconds. For each VEMP measurement, the response to at least two separate sequences of 500 clicks was averaged at least twice.

All participants received a comprehensive explanation of the procedure and gave their informed consent before testing. The Israel Defense Forces Medical Corps Human Research Committee approved the study protocol and testing procedures.

The following parameters were compared between the two groups: bilateral presence of the first compound peak (P13-N23) of the VEMP ipsilateral to the stimulated ear (Fisher’s exact test), average P13 and N23 wave latencies and amplitudes, and the P13-N23 inter-peak latencies (simple t-test). When VEMP response was elicited at least in one ear, side differences in peak-to-peak amplitude were calculated and expressed as an asymmetry ratio according to the following calculation:

\[
\text{Asymmetry Ratio} = \left(\frac{\text{Amplitude}_{Lt} – \text{Amplitude}_{Rt}}{\text{Amplitude}_{Lt} + \text{Amplitude}_{Rt}}\right) \times 100.
\]

Asymmetry ratios up to 35% have been found in normal subjects under the age of 60 [14]. The average asymmetry ratio and the number of subjects with a ratio greater than 35% were compared between the groups. For all the statistical tests a \( P \) value < 0.05 was taken to indicate statistical significance.

Results

Of the 10 susceptible subjects, 7 (70%) showed no VEMP responses in either ear, 2 (20%) showed a response in one ear only, and 1 (10%) showed a response in both ears. Of the 14 non-susceptible subjects, 4 (28.6%) showed no response in either ear, 3 (21.4%) showed a response in one ear, and 7 (50%) showed a reproducible response in both ears. The difference between the groups in the number of subjects in whom bilateral VEMP response could be produced did not reach statistical significance (\( P = 0.08 \), Fisher’s exact test).

Table 1 shows the mean and standard deviation of P13 and N23 peak latencies, amplitudes, and peak-to-peak amplitudes for each ear in each group. There were no statistically significant differences between the two groups in VEMP wave absolute and inter-peak latencies, wave amplitudes, and asymmetry ratios. The number of subjects with an asymmetry ratio greater than 35% was larger in the susceptible group, but this difference was not statistically significant (\( P = 0.07 \), Fisher’s exact test).

Discussion

The main finding in this study was the lack of statistically significant differences in VEMP response parameters between the two groups. The absence of VEMP response in most of the

Table 1. VEMP parameters (mean ± SD) of the seasickness susceptible and non-susceptible groups*

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<th>Right ear</th>
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<th>Left ear</th>
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<tr>
<td></td>
<td>Susceptible</td>
<td>Non-susceptible</td>
<td>Susceptible</td>
<td>Non-susceptible</td>
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<tr>
<td>P13 latency</td>
<td>13.01 ± 2.57</td>
<td>14.28 ± 2.55</td>
<td>17.85 ± 2.52</td>
<td>15.12 ± 2.87</td>
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<tr>
<td>P13 amplitude</td>
<td>5.18 ± 1.42</td>
<td>6.67 ± 5.99</td>
<td>3.7 ± 2.04</td>
<td>6.45 ± 6.42</td>
</tr>
<tr>
<td>N23 latency</td>
<td>20.18 ± 2.62</td>
<td>21.49 ± 2.28</td>
<td>23.48 ± 1.96</td>
<td>21.27 ± 3.17</td>
</tr>
<tr>
<td>Peak-to-peak amplitude</td>
<td>7.15 ± 3.04</td>
<td>7.21 ± 3.99</td>
<td>5.63 ± 0.56</td>
<td>6.16 ± 2.39</td>
</tr>
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* Latency is given in msec and amplitude in \( \mu \text{V} \).
susceptible subjects when compared to the non-susceptible group, although not reaching statistical significance, could indicate a reduction of saccular function or attenuated response to saccular activation in this group. This could be the result of primary response characteristics in the susceptible group leading to greater reliance on visual and somatosensory inputs during exposure to linear acceleration or head tilt, or secondary to an acquired decreased dependence on vestibular input.

Previous studies of vestibular organ function and of the input from the vestibular organs during exposure to extreme motion conditions have shown dynamic changes dependent on these conditions. Reschke and colleagues [15] showed significant changes in posture tests in pilots after adaptation in sustained microgravity conditions, demonstrating a direct effect of the altered otolith input on postural reflexes. Studies comparing postural stability in astronauts, before and after space flight, using computerized dynamic posturography have shown less post-flight reliance on vestibular input for the maintenance of balance [16]. After returning to normal gravity conditions, a gradual return to normal function was observed. These findings support the notion that changes in balance strategy are secondary to exposure to different gravitational conditions and do not result from a primary vestibular dysfunction.

Studies of seasickness and mal de debarquement, characterized by an inappropriate movement sensation after returning from prolonged sailing, have found changes in the vestibulo-ocular reflex and in the balance strategy. Shupak and co-authors [17] found an increased vestibulo-ocular reflex gain and phase lead in susceptible subjects during habituation to sea conditions. Shahal et al. [18] found that susceptible subjects rely less on vestibular input for stability as determined by CDP testing. Nachum and team [19] reported that in subjects with mal de debarquement, there is less reliance on visual and vestibular input for the maintenance of balance and more reliance on somatosensory input.

The results of the microgravity studies in pilots and astronauts as well as the results of the seasickness and mal de debarquement studies are in agreement with the tendency for reduced saccular function among the susceptible subjects in this study. This may be explained by reduced vestibular function as part of the larger adaptation effort to the neural conflict in the susceptible subjects.

According to recent studies all situations that provoke motion sickness are characterized by a condition in which the sensed vertical, as determined on the basis of integrated information from the visual system, the vestibular system and the non-vestibular proprioceptors, is at variance with the subjective vertical as expected from previous experience [4]. In this context, reduced otolithic function would abolish the conflict between the sensed and subjective vertical and could be considered part of the habituation effort in unusual motion conditions. On the other hand, it is possible that impaired or asymmetric otolithic function would lead to a further discrepancy between the sensed and expected vertical and to an increase in motion sickness susceptibility. Von Baumgarten and colleagues [20] have suggested that asymmetries in otolithic function between the two labyrinths, which result from different masses of the otoconia, cause motion sickness. Under normal terrestrial conditions, central compensation would balance and normalize the different discharge characteristics of the otolithic organs. On exposure to unusual motion patterns, this compensation would no longer be appropriate and until the resulting functional asymmetry readjusts, motion sickness would occur. In support of the otolithic asymmetry hypothesis, subjects with large asymmetries between their ocular counterrolling responses for leftward and rightward body tilts were found to be significantly more susceptible to motion sickness when passively exposed to variations in gravito-inertial force load [21-23]. Significant differences between the otocorial mass in the left and right labyrinths were found in fish that exhibited an uncoordinated or passive swimming pattern when exposed to Coriolis force environment, when compared to fish that maintained an active compensatory swimming behavior under the same conditions [14,24]. In this study a larger proportion of susceptible subjects met the criterion for peak-to-peak amplitude side asymmetry greater than 35%, although the differences between the groups showed only a trend towards marginal statistical significance.

Conclusions

The results of the study might be interpreted as reflecting a trend toward attenuation of saccular function as part of the habituation process to sea conditions. Also, asymmetry in VEMP response could be related to increased intravestibular conflict, thus greater vulnerability to seasickness. Further studies with larger numbers of subjects are necessary to validate the tendency towards reduced saccular response and increased side asymmetry in seasickness-susceptible subjects.

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References

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**Capsule**

**Immune reconstitution syndrome associated with opportunistic mycoses**

Host immunity is essential in facilitating the eradication of infection. However, immunological recovery and an imbalance characterized by either suboptimum or excessive expression of immune responses can also be harmful to the host. Inflammatory responses triggered by rapid resolution of immunosuppression can lead to a series of localized and systemic reactions, termed immune reconstitution syndrome (IRS), which are often misconstrued as failure of specific antifungal therapy to eliminate the offending fungal pathogen. Recognition of IRS has become increasingly relevant in the context of our current use of potent immunosuppressive agents and immunostimulators, which allow rapid manipulation of the immune system. Whereas the conceptual principles of IRS underscore the adverse effects of an overzealous and dysregulated immune response, they also support a role of immunotherapies to augment immunity if induction of endogenous responses is inadequate for the control of infection.

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**Capsule**

**Allergy-blocking transmitters**

The endocannabinoid system performs various regulatory functions and has been implicated in a growing number of physiological roles, both in the central and peripheral nervous systems and in peripheral organs. Karsak and associates found that this influence extends to regulation of allergic response. Mice lacking the two known cannabinoid receptors showed a strong tendency toward developing cutaneous contact sensitivity in response to distinct allergens. Blocking the receptors with antagonists had a similar effect, while absence of the gene encoding an enzyme responsible for breaking down cannabinoids increased resistance of mice to contact sensitivity. The regulation of the endocannabinoids or their receptors might be useful in treating allergies, although their role in the wider context of human allergy needs to be explored.

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