Vertigo and motion sickness. Part I: Vestibular anatomy and physiology

Timothy P. Zajonc, MD; Peter S. Roland, MD

Abstract
Control of the symptoms of vertigo and motion sickness requires consideration of the neurophysiology of areas both intrinsic and extrinsic to the vestibular system proper. We review the essential anatomy and physiology of the vestibular system and the associated vomiting reflex.

Introduction
Vertigo is often accompanied by visceral autonomic symptoms, including pallor, diaphoresis, nausea, and vomiting. Vertigo is similar to motion sickness in that both can be caused by vestibular stimulation that does not match an internal model of expected environmental stimuli. Indeed, a functioning vestibular system is necessary for the perception of motion sickness. For this reason, many of the same drugs are used to treat both conditions. Selection of a particular type of drug therapy can be facilitated by an understanding of the essential anatomy and physiology of the vestibular system and the associated vomiting reflex.

Vestibular pathways
The receptor cells for vestibular stimuli are the hair cells of the vestibular labyrinth. Type I hair cells are flask-shaped and connected to a single large afferent nerve fiber. Type II cells are cylindrical, and they are innervated by a series of bouton-type nerve endings at their base. These sensory cells are found in the cristae at the ampullated ends of the semicircular canals and in the maculae of the utricle and saccus. Movement of the endolymph in the semicircular canals, and movement of the otoliths in the case of the maculae, is translated by the hair cells into an electrical impulse. This impulse is propagated by the afferent nerves toward the vestibular nuclei. There are four vestibular nuclei: the superior vestibular nucleus, the lateral vestibular nucleus, the medial vestibular nucleus, and the descending vestibular nucleus. Secondary vestibular afferent fibers are responsible for making connections with the contralateral vestibular nuclei, oculomotor control areas, the cerebellum, and the spinal cord.

The chief neurotransmitter in the vestibular nuclei is believed to be the excitatory amino acid glutamate. Electron-microscope autoradiography demonstrates glutamate uptake sites in the lateral and inferior vestibular nuclei of cats. The number of these sites is significantly decreased by previous sectioning of the vestibular nerve, indicating that glutamate is involved in the transfer of signals from vestibular afferent neurons. Glutamate actions are mediated by excitatory amino acid receptors. The four main families of excitatory amino acid receptors are α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA), N-methyl-D-aspartate receptors (NMDA), metabotropic glutamate receptors, and kainic acid receptors. AMPA, NMDA, and metabotropic receptors have been found in the vestibular nuclei. Glutamate appears to act primarily on AMPA-type receptors in the vestibular nuclei.

Acetylcholine has been identified in primary vestibular afferents of the vestibular nuclei. In cat studies involving measurements of the field potential of the lateral vestibular nucleus, the application of acetylcholine produces the same response as does stimulation of the vestibular nerve. In addition, the response to stimulation of the vestibular nerve is enhanced by inhibition of acetylcholinesterase and blocked by the antimuscarinic drug scopolamine. Muscarinic receptors are acetylcholine-binding receptors that have historically been demonstrated to be activated by muscarine and blocked by atropine.

Knowledge of muscarinic receptor subtypes and their pharmacologic actions is increasing, and more effective anticholinergic medications with fewer side effects are in development. There are now five known structural subtypes of muscarinic receptors, designated M1 through M5. The capitalized designations M1, M2, and M3 represent pharmacologic definitions, which are based on the actions of various drugs that bind muscarinic receptors selectively. It has been shown that the structural designations M1 through M5 correlate with the pharmacologic definitions M1 through M5, respectively. In situ hybridization studies of rat brain have demonstrated a unique distribution of muscarinic...
receptor subtypes. The \( m_1 \) receptors are abundant in the cerebral cortex, striatum, and hippocampus. The \( m_2 \) receptors are very rare in brain tissue; they are found in significant quantities only in the medial septum and pons and in lesser amounts in the thalamus. The distribution of \( m_3 \) receptors is similar to that of \( m_1 \) receptors, but \( m_3 \) receptors are also found in several thalamic nuclei and brainstem nuclei. The \( m_4 \) receptors are found in the cortex, striatum, and hippocampus, and the \( m_5 \) receptors are found in very low levels in the hippocampus and some brainstem nuclei. Bovine brain studies have also revealed that muscarinic receptors are found in the vestibular nuclei.

Localization of receptor subtypes to specific areas of the brain allows for the possibility of designing drugs that have a more specific action.

Another regulatory substance in the vestibular nuclei is histamine. \( H_1 \), \( H_2 \), and \( H_3 \) receptors are present in the medial vestibular nucleus. Field-potential recordings demonstrate that the \( H_2 \) antagonist diphenhydramine decreases firing of polysynaptic pathways in the lateral vestibular nucleus.

Other inhibitory actions in the vestibular nuclei are mediated by \( \gamma \)-aminobutyric acid (GABA). Two subclasses of GABA receptors—GABA A and GABA B—are found in the vestibular nuclei. GABA A receptors are bound by benzodiazepines for agonist effects. GABA B receptors bind baclofen for agonist effects. Neurons from the contralateral vestibular nuclei and Purkinje fibers from the cerebellum are believed to exert their inhibitory effects via this GABAergic system.

Neurokinin type 1 (NK\(_1\)) receptors have been found in some vestibular afferents. NK\(_1\) receptors bind substance P, which is a neuroactive peptide. Substance P is thought to be involved in many actions throughout the body, including the transmission of painful stimuli, but its role in the vestibular system is unclear at this time.

Other receptors found in the vestibular nuclei include \( D_2 \) dopaminergic receptors, 5-HT\(_1\) and 5-HT\(_2\) (serotoninergic) receptors, and \( \alpha_2 \) - and \( \beta_1 \) -adrenergic receptors (table).

Norepinephrine, which binds adrenergic receptors, has been reported to block neuronal firing in the medial vestibular nucleus while it stimulates neurons in the lateral vestibular nucleus.

The cerebellum

The cerebellum is believed to function as a regulator of movement and posture by comparing movement intention with movement performance and regulating the actions of descending motor neurons. Information gathered on movement intention is called internal feedback. Sensory information about motor performance is called external feedback. Vestibular stimuli, representing spatial orientation, are also regarded as external feedback. The cerebellum compares internal and external feedback signals in order to regulate performance. The cerebellum is also believed to contain a conceptual internal model that reflects normal sensory congruities for a given movement or posture. When the comparison of the internal and external feedback signals does not fall within the parameters of this internal model, a sensory mismatch is said to exist. These sensory

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Area postrema</th>
<th>PCRF/NTS</th>
<th>Cerebellum</th>
<th>Vestibular nuclei</th>
<th>Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPA/NMDA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Muscarinic</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Histaminic</td>
<td>( H_2 )</td>
<td>( H_1 )</td>
<td>( H_1 )</td>
<td>( H_1, H_2, H_3 )</td>
<td></td>
</tr>
<tr>
<td>GABAergic</td>
<td>GABA A</td>
<td>GABA A</td>
<td>GABA A, GABA B</td>
<td>GABA A, GABA B</td>
<td>GABA A, GABA B</td>
</tr>
<tr>
<td>Dopaminergic</td>
<td>( D_2, D_3 )</td>
<td>( D_2, D_4, D_4 )</td>
<td>( D_3 )</td>
<td>( D_2 )</td>
<td>( D_1, D_2, D_4, D_3 )</td>
</tr>
<tr>
<td>Serotoninergic</td>
<td>5-HT(_3)</td>
<td>5-HT(_{1A}, 5-HT(_3)</td>
<td>5-HT(_2)</td>
<td>5-HT(_{1A}, 5-HT(_2)</td>
<td>5-HT(_2)</td>
</tr>
<tr>
<td>( \alpha )-Adrenergic</td>
<td>+</td>
<td>+</td>
<td>( \alpha_2 )</td>
<td>( \alpha_2 )</td>
<td>( \alpha_2 )</td>
</tr>
<tr>
<td>( \beta )-Adrenergic</td>
<td>+</td>
<td>+</td>
<td>( \beta_1 )</td>
<td>( \beta_1 )</td>
<td>( \beta_1, \beta_2 )</td>
</tr>
</tbody>
</table>

Key: PCRF = parvicellular reticular formation; NTS = nucleus tractus solitarius; AMPA = \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NMDA = N-methyl-D-aspartate; GABA = \( \gamma \)-aminobutyric acid.
mismatches can develop as a result of new environmental stimuli or erroneous input caused by disease. Upon the detection of a mismatch, uncomfortable sensations such as disequilibrium, vertigo, or motion sickness occur. The cerebellum is thought to promote short-term regulation and long-term habituation to compensate for these mismatched signals.16

The idea that the cerebellum functions as a regulator of the vestibular system is supported by the observation that lesions of the cerebellar flocculus inhibit adjustments to the gain of the vestibulo-ocular reflex.16,17 Also, when nodullectomy was performed on cats, previously acquired habituation to caloric stimulation was lost. This lesion also severely interfered with the cats’ further acquisition and retention of habituation.18 Additionally, dogs have been rendered immune to motion sickness by ablation of the nodus and uvula of the cerebellum.19,20

Neurons projecting from the inferior olivary nucleus to the cerebellar nuclei and cerebellar cortex are also necessary for vestibular compensation. The inferior olivary neurons are believed to carry information about voluntary motor movements. Destruction of the inferior olive in rats prevents compensation after unilateral labyrinthectomy.1,21

Vomiting center
The area of the brainstem known as the parvicellular reticular formation (PCRF) is believed to function as the vomiting center, where the vomiting reflex is initiated and coordinated. Electrical stimulation of this area in cats has been shown to evoke vomiting.1,22 The PCRF is located ventral to the vestibular nuclei and medial to, as well as partially coextensive with, the elongated nucleus of the spinal tract of the trigeminal nerve. The PCRF projects fibers to the motor nucleus of the facial nerve, to the hypoglossal nucleus, and to the parabrachial nuclei, which contain some respiratory centers.1 These connections may allow for coordination of the vomiting reflex. Also, the PCRF is traversed by an extensive system of commissural fibers that interconnect the vestibular nuclear complexes. It has been suggested that fine axon collaterals may arise from these commissural fibers to connect the PCRF to the vestibular nuclei. There are many other cortical and subcortical afferent connections to the PCRF, but the exact means by which these pathways are integrated and this information is used to initiate vomiting are not clear.1

The nucleus tractus solitarius is closely related to the PCRF. It serves as a major coordinating center for autonomic functions in the brainstem and undoubtedly plays a significant role in the vomiting reflex. It receives vagal, vestibular, area postrema, and limbic inputs.4 The nucleus tractus solitarius is rich in catecholamine-containing fibers, has dense GABA input, and also contains 5-HT1a receptors.

Area postrema
The area postrema is located laterally along the floor of the fourth ventricle; it is not protected by the blood-brain barrier. Early studies in dogs showed that ablation of this area prevented motion sickness. Later studies in both cats and squirrel monkeys, which might have involved more accurate ablation of the area postrema, demonstrated no protection from motion-induced emesis.1 The facts that stimulation of the area postrema produces vomiting in cats and that it is not protected by the blood-brain barrier suggest that the area postrema contains the chemoreceptor trigger zone for the production of vomiting in response to noxious chemicals.
Organizational model
The currently understood model for the production of vertigo or motion sickness includes a system in which information is gathered from vestibular, visual, proprioceptive, and cortical activity (figure). This information is then compared with an internal model of expected input congruity. Detection of a stimulus mismatch promotes the symptoms associated with vertigo and motion sickness. This comparator also serves to promote habituation to new environmental stimuli or compensation for erroneous input caused by disease.

It is interesting that some medications that are excellent antiemetics do not prevent vertigo or motion sickness. One such medication, ondansetron, is often used for the prevention of chemotherapy-induced nausea. It acts on 5-HT3 receptors in the area postrema. Activity in this location would not necessarily prevent stimulation of the vestibular nuclei from ultimately causing nausea and vomiting. However, patients who are particularly susceptible to motion sickness also demonstrate increased responses to other vomiting center stimuli. This may provide a rationale for the use of general antiemetics in vertigo associated with nausea.23-24

The role of medications in treating vertigo and motion sickness will be reviewed in part II of this article in an upcoming issue.

References