Diagnosis and Treatment of Vestibular Disorders

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Preface

Vestibular disorders can result in devastating and frightful symptoms, creating dramatic changes in immediate and long-term quality of life. Diagnosis and management of the patient afflicted with vestibular disorders is rewarding to the patient and the physician. This task is complex and begins with a thorough clinical history and neurotologic physical examination. With a judicious use of diagnostic tests, a diagnosis may be obtained in the majority of patients. Afterward, an effective treatment plan can be initiated.

Patients with dizziness present to the primary care physician, the emergency room physician, the neurologist, or the otolaryngologist. This textbook was developed for these physicians in order to provide a useful, practical approach to evaluate and treat patients with dizziness. Its intent is to improve the ability to accurately diagnose specific vestibular disorders, initiate appropriate therapy, reduce the unnecessary cost burden by knowing when to refer, and most importantly improve patient's quality of life.

To accomplish this task, the book is separated into several parts. The anatomy and physiology of the vestibular system is discussed to provide a necessary background for the disease process. A thorough history and neurotologic examination is described to allow implementation into practice. Audiologic and vestibular testing is described in order to facilitate appropriate referrals and interpretation of test results. Finally, pathophysiology, diagnosis, and management strategies for common vestibular diseases are discussed with an evidence-based review.

Understanding the vestibular system and disorders began centuries ago and continues to evolve to this day. Some notable influences include Prosper Meniere, Ernst Ewald, and Robert Barany. In 1861, Meniere, a French researcher, described a series of patients with episodic vertigo and hearing loss, placing the inner ear as the pathologic source of the vertigo. In the late 1800s, Ernest Ewald, a physiologist from Germany, established the labyrinthine origin of nystagmus and described eye movement correlated with vestibular involvement. Robert Barany, an Austro-Hungarian otologist who won the Nobel Prize in 1914, developed testing theories and methods

of testing the labyrinth. Continuation of identification of new vestibular disorders has occurred as recent as 1998 with the description of superior canal dehiscence by Lloyd Minor.

The field of neurotology became a subspecialty thanks to the foresight, research, and unselfish dedication to teaching of many physicians. William House is considered the father of neurotology with his endeavors in the care of acoustic neuromas, treatment of the patient with vestibular disorders, and development of the cochlear implant. His unselfish and tireless efforts to share his knowledge with temporal bone laboratory teaching and the beginning of a fellowship program to teach this subspecialty to otolaryngologists is unparalleled. His approaches and management matured and spread to hundreds of physicians throughout the world. Michael Glasscock and Malcolm Graham, who both trained at the House Ear Institute, brought skull base surgery to the Midwest in Nashville, TN, and Detroit, MI, respectively. Harold Schuknecht began his work with T. Manford McGee at Henry Ford Hospital prior to Schuknecht moving to Massachusetts Eye and Ear Infirmary and McGee staying in the greater Detroit area. The Michigan Ear Institute would later be formed with Drs. Graham, McGee, Kartush, Bojrab, and LaRouere and Charles Stockwell, PhD, and Ken Bouchard, PhD.

All of these physicians, teachers, and researchers had the unrelenting desire to optimize patient care and spread knowledge through temporal bone laboratory teaching and fellowship training programs, thus allowing them to propagate the standard of care that will continue to carry on for years to come. In addition to the abovementioned physicians, we owe much of our understanding of clinical signs and diagnostic tests of the patient afflicted with vestibular disorders to such people as Hugh Barber, Vincente Honrubia, Robert Baloh, David Zee, John Leigh, and John Carey, to name a few.

We feel fortunate to have many esteemed colleagues from around the country willing to commit their tireless dedication to provide their insight and education to make this textbook better than we thought possible. To them we are grateful.

> To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all. – Sir William Osler

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Part I
The Vestibular System

Chapter 1
Anatomy and Physiology of the Vestibular System

Ashley C. Zaleski-King, Wanda Lai, and Alex D. Sweeney

Introduction

The human vestibular system facilitates proper balance by sensing and integrating movement. In general, vestibular anatomy and physiology can be divided into peripheral and central components. This chapter summarizes the structural organization and the physiological processes relevant to the functioning of the vestibular system in healthy individuals.

Anatomy and Physiology of the Peripheral Vestibular System

The peripheral vestibular system contains five sensory structures: three semicircular canals (the horizontal, also termed lateral; anterior, also termed superior; and posterior canals) and two otolith organs (the utricle and the saccule). Within each sensory organ, sensory hair cells are organized specifically to allow for transduction of head motion in different planes into neural impulses (Fig. 1.1).

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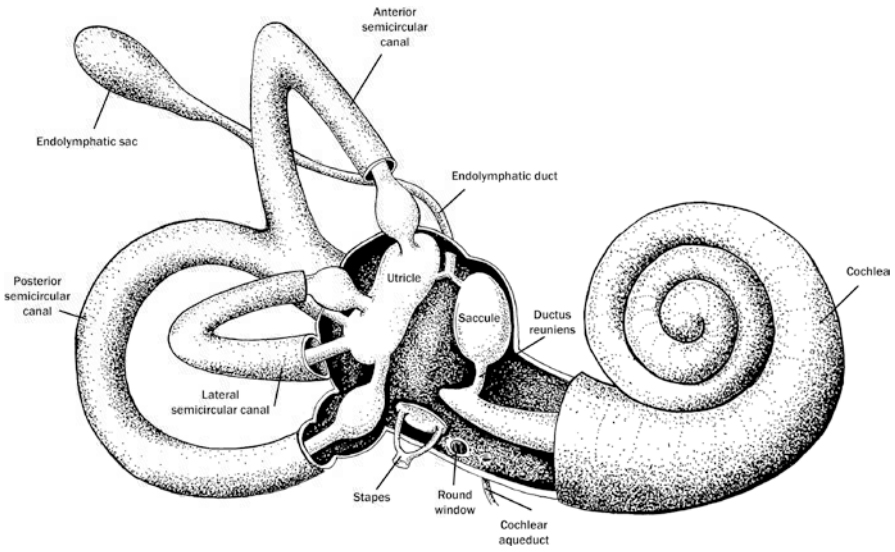

Fig. 1.1 Anatomy of the labyrinth

The Inner Ear Labyrinths

The peripheral sensory apparatus of the vestibular system lies within the inner ear, laterally adjacent to the air-filled middle ear, medially bordered by the temporal bone, posterior to the cochlea. Within the inner ear, a bony labyrinth houses a membranous labyrinth containing vestibular receptors. The two labyrinths differ in the type of fluid composition. The bony labyrinth contains perilymph, which is a substance with chemical composition similar to cerebrospinal fluid, with an increased sodium-to-potassium concentration ratio [30]. The cochlear aqueduct is thought to connect perilymph to the spinal fluid pathway. The oval window and the round window are two structures separating the middle ear and the perilymph of the inner ear.

The membranous labyrinth contains endolymph, a second type of inner ear fluid. Endolymph is composed of a higher potassium-to-sodium concentration ratio, similar to intracellular fluid [15]. Endolymph is generated in the stria vascularis in the wall of the cochlear duct [26]. The endolymphatic sac, a membranous structure within the inner ear, absorbs endolymph and connects to other endolymphatic spaces within the inner ear through the utricular duct and the ductus reuniens [8]. Separation of endolymph and perilymph fluids is maintained through a tight junctional complex surrounding the apex of each cell [16]. Partitioning of the fluids is important for mechanical reasons, to allow semicircular canals to utilize endolymph fluid dynamics to transmit semicircular canal information, and also for biophysiological reasons, to provide an electrochemical gradient necessary for hair cell transduction [16]. Though outside of the scope of this chapter, it is also noteworthy that the structural integrity of this partition is also essential to the biological basis of auditory function in the inner ear.

Inner Ear Sensory Hair Cells

Each vestibular structure contains specialized sensory hair cells. These hair cells function to transmit mechanical energy into neural activity generated as a result of head motion or as a result of gravitational changes [9]. Head motion occurs with linear and/or rotational acceleration forces that cause deflection of a specific subset of hair cell bundles in each receptor organ.

Vestibular receptor hair cells consist of cilia, the cell body, and nerve endings (afferent and efferent). The cilia are rod-shaped sensory mechanoreceptors embedded in a membrane of neuroepithelium, forming a rigid bundle on top of each cell body. The basic structure of each hair cell includes a single, long hair kinocilium, and approximately 70–100 shorter hairs, stereocilia, on the apical end [27]. These hair cells are organized in rows and positioned based on length. The tallest stereocilia are positioned in the closest and the shortest in furthest proximity to the kinocilium. Tip links are filamentous structures that connect the tips of shorter stereocilia to the body of adjacent taller stereocilia [3].

The vestibular epithelium consists of two different types of cell bodies: type I and type II. Type I hair cell bodies are shaped like a flask with a rounder base, wider middle, and narrower apex and base. The calyx, a large afferent nerve ending, surrounds the type I hair cell body and makes contact with efferent nerve ending. Type I hair cells are associated with irregular afferent activity and high variability in resting discharge rate. Type II hair cells are the most abundant and are shaped like a cylinder with several afferent and efferent direct connections. Type II hair cells mostly synapse on regular afferents with low variability of resting discharge rate. Differences in type I and type II hair cell adaptation may be related to differences in attachment of afferent and efferent nerve endings [1].

Though structurally different, type I and type II hair cells share important functional features. Both hair cell types generate a tonic, spontaneous neural firing rate averaging around 70–90 spikes per second [12] in the absence of any stimulus (Fig. 1.2). Both types of hair cells also exhibit excitatory and inhibitory responses, though only when the hair cell bends in a plane of polarization specific to that cell body. This directional polarization functions so that during excitatory responses, deflection of stereocilia causes bending toward the kinocilium. This movement toward the kinocilium shifts the tip links, causing a mechanical opening of the transduction channels and an influx of potassium ions. Depolarization of the hair cell stimulates neurotransmitter release into the synapses, causing an increase in firing rate. This excitatory activity increases neural firing rate from the tonic level to up to 400 spikes per second. The opposite occurs during inhibition, when stereocilia are bent away from kinocilium, resulting in decreased tip link tension, mechanical closure of the channel, and a decrease in firing rate. In comparison to the change in neural firing rate during excitation, the change in neural activity during inhibition is significantly reduced from the tonic rate of around 90 spikes per second down to the disappearance of neural activity.

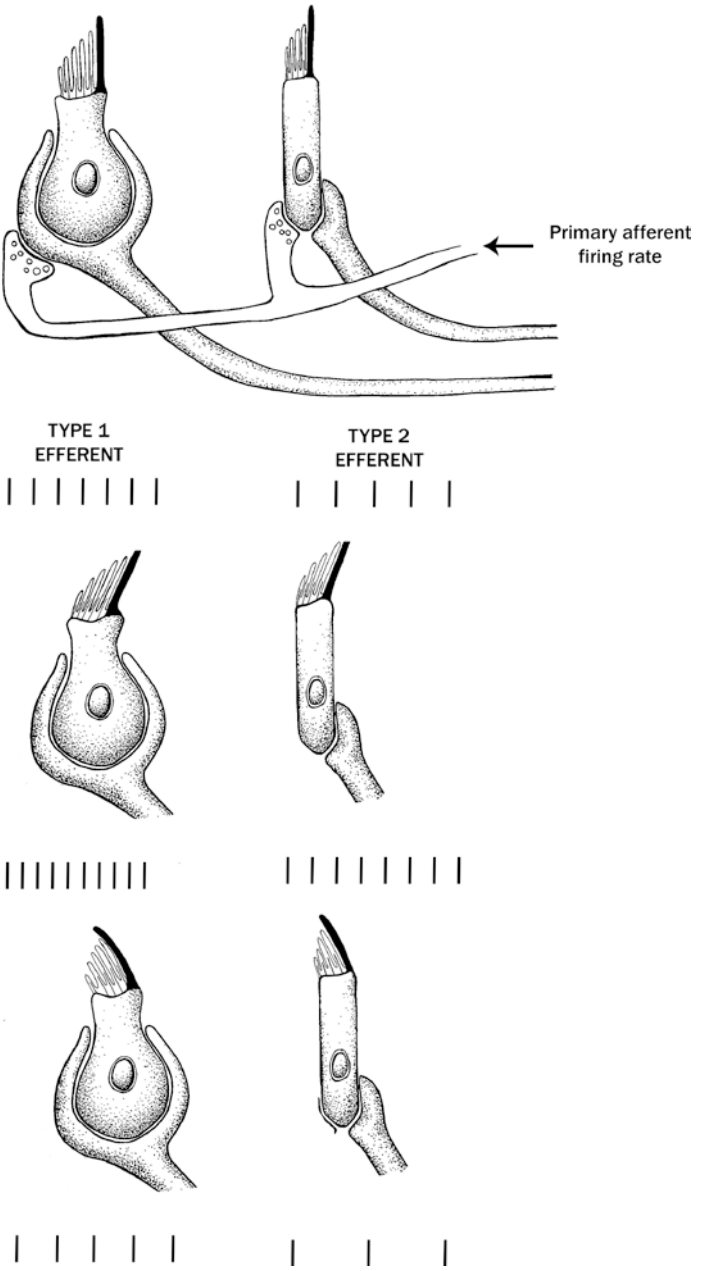

Fig. 1.2 Afferent firing rate in basal state, toward kinocilium and away from kinocilium

Semicircular Canals

The three semicircular canals (SCCs) consist of the membranous labyrinth encased in bony canal structures, arranged in three mutually perpendicular planes. Together, the lateral (or horizontal), anterior (or superior), and posterior SCCs make up a unique arrangement that allows for a three-dimensional vector representation of rotational acceleration. Whereas the lateral canals are oriented in a 30° angle in the axial plane, the superior and posterior canals are oriented in a 45° angle to the sagittal plane [22]. Each SCC is sensitive to movement in a specific vector, residing in approximate parallel planes to the SCC in the opposite ear (i.e., the left ear lateral and right ear lateral, left ear anterior and right ear posterior, and left ear posterior and right ear anterior).

All SCCs open into the utricle; the other end of each SCC opens to the ampulla, a dilated sac [23]. At the base, the ampulla contains sensory neuroepithelium, the crista ampullaris, which is comprised of approximately 7000 hair cells. These hair cells are embedded into the cupula, a gelatinous surrounding attached to the epithelium at the base of the crista. The cupula can be thought of as a "plug" dividing the SCCs into two compartments [2]. Within the cupula, each hair cell makes synaptic contact with nerve endings to form the primary afferent nerve fiber of each SCC.

Within each SCC, hair cells are either oriented toward or away from the utricular sac, to generate either an excitatory or inhibitory response. In the lateral canal, for example, the kinocilia are positioned pointing toward the utricular sac. An excitatory response is generated when the cupula is bent toward the utricular sac, known as ampullopetal flow, and an inhibitory response is generated when the cupula is bent away from the utricular sac, termed ampullofugal flow. The opposite is true for hair cell orientation in the anterior and posterior SCCs: ampullopetal flow (i.e., cupula bending toward the utricular sac) results in inhibition and ampullofugal (i.e., cupula bending away from utricular sac) results in excitation.

The mechanics of SCC activation are related in part to the density and viscosity characteristics of the cupula and the surrounding endolymph [2]. The cupula and the surrounding endolymph are made up comparable densities [1]. Without head motion, hair cells embedded within the cupula remain at a neutral position as the cupula floats within the endolymph.

With head motion, rotational acceleration generates endolymph movement that displaces the cupula, bending hair cells in the opposite direction of rotation. The viscous makeup of endolymph causes fluid to lag behind, producing a current in the opposite direction of rotation. The cupula and the embedded stereocilia are then deflected and, based on the direction of rotation, produce either a sudden increase or decrease in neural firing rate of the afferent neuron (Fig. 1.3) [12]. When rotational velocity of the head becomes constant, the cupula returns to an upright position, and the synaptic potential of each cell normalizes [20]. The viscosity of the endolymph

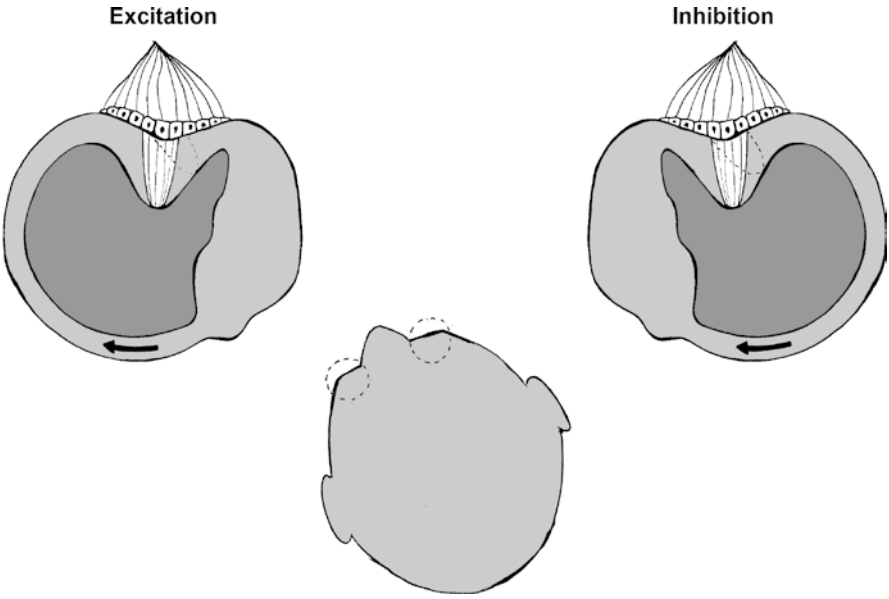

Fig. 1.3 Rotary head motion resulting in excitation and inhibition of respective paired semicircular canals

and the mass of the cupula dampen the neural firing rate, limiting the amount of head velocity information generated for low-frequency head motion. Canal responses are also limited in that they are asymmetrical at high frequencies due to the greater dynamic range of hair cells available during the excitatory response of hair cells [12].

Otolith Organs

The two otolith organs, the utricle and the saccule, are housed within two cavities in the vestibule. The utricle is oval-shaped and contained within a swelling adjacent to the SCCs, the elliptical recess. The saccule is oriented perpendicular to the utricle and parallel to the sagittal plane within the spherical recess. Together, the otolith organs function to detect linear acceleration and static orientation of the head relative to gravity.

The sensory neuroepithelium is contained within the macula of each otolith organ, oriented horizontally in the utricle and vertically in the saccule. The striola is an area within the neuroepithelium dividing hair cells into two regions with different hair cell arrays. Unlike the SCCs, the stereocilia within the otolith organs are polarized in different directions: away from the kinocilium in the saccule and toward the kinocilium in the utricle. These hair cell bundles project into a gelatinous membrane, on top of which are calcium carbonate particles, or otoconia, embedded on the surface.

Linear acceleration generates forces on the otoconia and gelatinous membrane, resulting in deflection of hair cell bundles. The utricle is stimulated by movement in the horizontal plane (i.e., head tilt sideways and lateral displacement), while the saccule is excited by movement in the vertical plane (i.e., sagittal plane upward, downward, forward, and backward; [36]). This shearing motion between the layer of otoconia and the membrane displaces the hair cell bundles, opening mechanically gated transduction channels in the tops of the stereocilia to depolarize the hair cell and cause neurotransmitter release [36]. This neurotransmitter release generates an increase in afferent neural firing rate. For other hair cells with different orientations, the same shear force results in either a decrease in firing rate or no change to the tonic firing rate [2]. A subset of afferent nerves fire specifically when the head is upright, before increasing or decreasing based on direction of head tilt [13].

Though conceptual and theoretical understanding of peripheral end-organ innervation is fairly straightforward, activation of these pathways is more complex and sometimes restricted. The otolith organs are limited in the capacity to distinguish between tilt with respect to gravity and linear translation [36]. In some cases, this inability to distinguish between translational accelerations and changes in head orientation can be resolved using extra-otolith cues arising from either the SCCs or the visual system [38]. In most cases, human movement results in simultaneous excitation and inhibition of both SCC and otolith receptor organs in both labyrinths.

Anatomy and Physiology of the Central Vestibular System

Central vestibular connections facilitate interaction of inputs from each vestibular labyrinth, as well as other inputs from somatosensory and visual sensory systems [15]. For example, a tilt to one side of the head has opposite effects of the corresponding hair cells of the other side of the head [36]. In addition, there is a convergence of otolith and semicircular canal input at all central vestibular levels, from the vestibular nuclei (VN) to cortical centers processing vestibular information [24].

The Vestibular Nerve

After peripheral end-organ excitation, labyrinthine sensory information is transmitted by the eighth cranial nerve through the internal auditory canal, entering the brain stem at the pontomedullary junction [15]. Along with the vestibular nerve, the facial nerve, the cochlear nerve, and the labyrinthine artery also travel through the internal auditory canal. Starting from the periphery, the bipolar neurons of Scarpa's (vestibular) ganglion are activated by the hair cells of the crista ampullaris in the SCCs and the maculae in the otoliths [3]. The superior portion of Scarpa's ganglion arises from the cristae of the lateral and anterior SCCs, the macula of the utricle, and a

branch of the saccular nerve. The inferior portion of Scarpa's ganglion connects to the cristae of the posterior SCC and the macula of the saccule. These superior and inferior bundles of Scarpa's ganglia merge with the cochlear nerve to form the eighth cranial nerve. Most vestibular nerve fibers connect centrally to the ipsilateral vestibular nuclei in the pons [5], though some innervate the cerebellum directly [2]. The central processing component begins as the eighth cranial nerve enters the brain stem, in the vestibular nucleus complex and in the cerebellum [15].

The Vestibular Nuclear Complex

The vestibular nuclei are located at the fourth ventricle and extend in two columns from the pons to the medulla. As the primary recipients of vestibular input, the VN include four major nuclei, the medial, superior, lateral, and inferior [5], which function to process vestibular input before transmission to motor centers [19]. In each ear, the vestibular nerve connects directly the ipsilateral VN, as well as to the contralateral side through several interconnecting neurons. The cerebellum, the reticular formation, the spinal cord, and the cervical junction all provide additional afferent information to the VN. Efferent information is relayed from the VN back to these same areas [2].

Motor Outputs of Vestibular System

Movement generates a complex pattern of vestibular stimulation. Information regarding head and body movement is transmitted through the central nervous system to motor centers such as the oculomotor nuclei and the spinal cord. The outputs of these systems allow individuals to walk while achieving a steady image on the retina through the vestibuloocular reflex (VOR) and to generate postural responses with respect to the external environments through the vestibulospinal reflex (VSR).

The Vestibuloocular Reflex (VOR)

The vestibuloocular reflex consists of a three-neuron arc. The reflex originates through peripheral organ activation, before connecting directly to the VN through the medial longitudinal fasciculus (MLF), the tract that carries excitatory projections from the abducens nucleus to the contralateral oculomotor nucleus. Indirect projections also arise from the reticular formation to the oculomotor nuclei. The purpose of the VOR is to preserve the image on the center of the visual field. This is accomplished through transduction of physical acceleration of the head into biological signals directing eye movement in the equal and opposite direction of head movement (Fig. 1.4) [29].

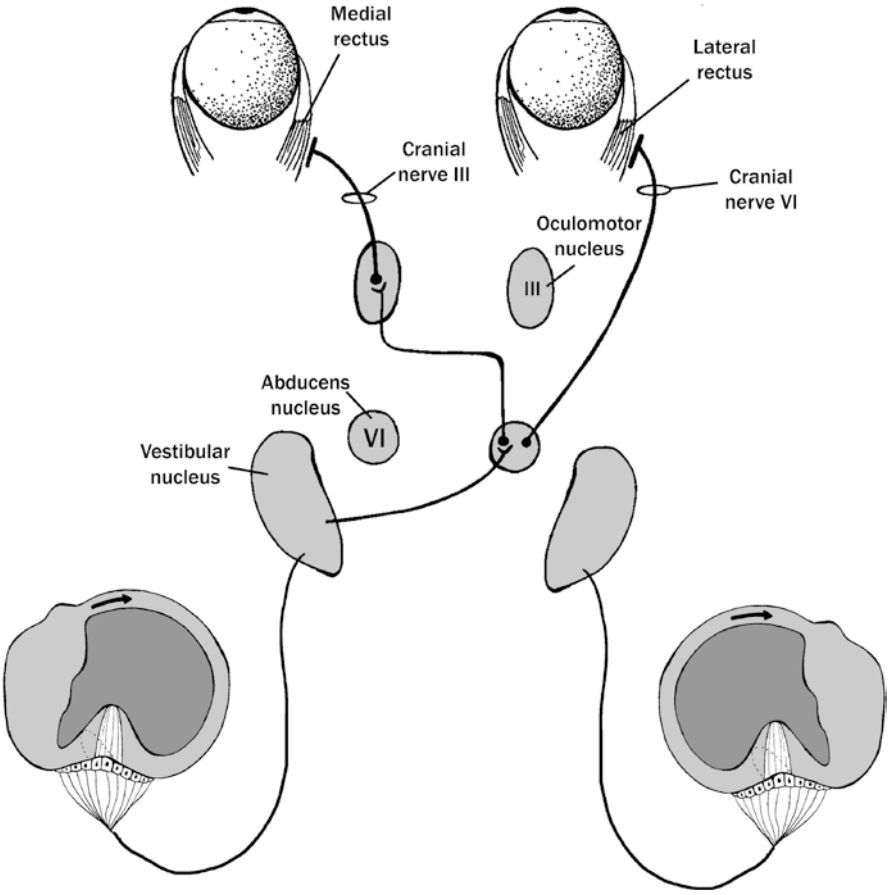

Fig. 1.4 Semicircular canal-ocular reflex

The latency of the VOR pathway is only around 20 ms [6, 7, 18], allowing rapid and accurate stabilization of gaze without any blurring of vision during head movements. The VOR completes this reaction quickly, but imperfectly, lacking in sensitivity to slow rotations. The VOR also compensates poorly for sustained motion at constant speeds. When there is no longer vestibular input during prolonged motion in light, two overlapping visual pathways, the optokinetic and the smooth pursuit systems, supplement vestibular responses. The velocity storage system, a central phenomenon which extends the duration of rotational vestibular signals, also helps. This system improves the ability of the (rotational) VOR to transduce low-frequency components of sustained head movements [21].

Six extraocular muscles are innervated to preserve the retinal image through three distinct nuclei: the oculomotor nucleus, the trochlear nucleus, and the abducens nucleus. Each muscle is balanced in such a way that the contraction of one

occurs simultaneously with the relaxation of another. Each pair works synergistically and coincides approximately with the planes of the SCCs. The VOR can be organized into three different subtypes based on planar function: the horizontal (or rotational) VOR, which compensates for head rotation; the translational VOR, which compensates for linear head movement; and the ocular counter-roll, which compensates for head tilt [36].

The rotational VOR functions as the head turns, activating the SCC. During horizontal rotation primary vestibular afferents from the horizontal SCC stimulate the ipsilateral medial and ventrolateral vestibular nuclei. These secondary vestibular neurons have axons that either decussate and ascend contralaterally to the abducens nucleus or ascend ipsilaterally to the oculomotor nucleus. The motor neurons from the abducens nucleus synapse at the lateral rectus muscle, whereas similar motor neurons from the oculomotor nucleus synapse at the medial rectus muscles. Some neurons also connect directly from the VN to the ipsilateral medial rectus through the ascending tract of Deiters. In addition to the excitatory projections, inhibitory projections also project to the ipsilateral lateral rectus and contralateral medial rectus muscles to permit eye movement in the equal and opposite direction of head movement [36]. Vertical SCC activation functions similarly. Activation of the anterior and posterior SCCs stimulates the VN which synapse on the oculomotor, trochlear, or abducens motor neurons. These synapses innervate the inferior and superior rectus and oblique muscles.

Relative to the rotational VOR pathway, less is understood about the translational VOR pathway, and specifically, the VOR pathway resulting in the ocular counter-roll response. Stabilization of an image when the head moves sideways, forward, or is tilted is thought to be due to the otolith-ocular pathway, connecting signals from the utricle and saccule to the oculomotor neurons [36]. During linear head translation, stimulation of the lateral portion of the utricle is mediated by polysynaptic connections to the lateral and medial VN. These VN synapses project to the abducens nucleus, bilaterally through the MLF to motor neurons directing eye gaze.

During head tilt, torsional or oblique eye movements produce an ocular counter-roll [25]. The ocular counter-roll consists of eyes moving in the opposite direction of the head tilt at a much smaller amplitude of the head tilt [28]. With head tilt, the medial portions of the utricle are excited, synapsing on the lateral VN. Through the MLF, the lateral VN connect to trochlear-oculomotor nuclei, which excite ipsilateral superior oblique and superior rectus and contralateral inferior oblique and inferior rectus muscles to generate ocular counter-roll. Ipsilateral projections from the VN also innervate polysynaptic inhibitory connections to the ipsilateral inferior oblique [35]. Static ocular counter-roll compensates for about 10–20% of the head roll in humans (with interindividual and intraindividual differences; [37]).

Vestibulospinal Reflex (VSR)

The vestibulospinal reflex (VSR) is composed of a series of motor commands, initiated from the vestibular system to help maintain postural stability. Visual and proprioceptive sensory inputs are integrated with information from the VSR to maintain orientation of the body relative to the external environment [17]. The VSR is composed of the medial and lateral vestibulospinal tracts in addition to the reticulospinal tract.

The medial vestibulospinal tract (MVST) is primarily a contralateral pathway, originating in response to simulation from the SCCs, through the medial VN. This pathway descends through the MLF bilaterally and terminates no lower than the mid-thoracic spinal cord [32, 33]. The MVST is thought to mediate head position by controlling the muscles of the neck and shoulder. Another reflex controlling head position through neck muscles is the vestibulocollic reflex. The vestibulocollic reflex stabilizes the head by initiating head movement in the direction counter to the current head-in-space velocity through activation of vestibular receptors [10]. Yaw rotation of the head typically involves SCC activation through vestibulocollic innervation to the medial VN, descending through the MLF to the upper cervical levels of the spinal cord [29].

The lateral vestibulospinal tract (LVST) includes ipsilateral excitatory pathways which originate in the lateral VN, descending through the inferior VN, to terminate on the anterior horn cells at various levels of the spinal cord and on proximal limb extensors. Simultaneous disynaptic connections inhibit contralateral proximal extensors [27]. The LVST is thought to control postural lower limb adjustments to movement. When the head is tilted, VN in both the canals and the otoliths are activated, transmitting impulses through the LVST and MVST to the spinal cord; this action induces extensor activity on the ipsilateral head side and flexor activity on the contralateral side [15]. The third pathway originating in the reticular formation descends to the spinal cord terminating in the mediate parts of the gray matter to influence limb and trunk movement. Both VN and the reticular formation provide information to the spinal cord to maintain compensatory feedback responses to postural instability.

Vestibulocerebellum

The vestibulocerebellum is also known as the flocculonodular lobe and is composed of the nodule and the flocculus. Afferent projections from the VN connect directly to the vestibulocerebellum. Efferent projections from Purkinje cells within the vestibulocerebellum send efferent information ipsilaterally to the VN and to the

fastigial nucleus. These pathways work to monitor vestibular activity and, when necessary, to support the vestibulocerebellar role as an adaptive processor. The vestibulocerebellum, for example, modifies vestibular input by adjusting the gain and duration of the VOR [20] while processing afferent activity from the macula [15]. This area also plays a role in translating vestibular and proprioceptive inputs to regulate vestibulospinal reflexes.

Vestibular Cortical Centers

In the primate brain, no isolated vestibular cortex has been identified [33]; however, the parietal insular vestibular cortex (PIVC) is one area of the cortex with a known concentration of vestibular inputs [34]. In macaques, neural activity in the PIVC has been recorded during head movement, in a position with the neck twisted and throughout motion of a visual target; similar PIVC activation is not associated with eye movement [34]. It is hypothesized that neurons in the PIVC may primarily be used as an index of movement in space to transform object movement from being self-referenced to being referenced to the environment [34].

Neurons in the PIVC also function to converge multisensory self-motion cues with external object motion information [31]. Vestibular inputs share cortical projections with other pathways processing visual and somatosensory information [11, 14]. Inhibitory vestibular-visual interaction has also been noted using large-field optokinetic visual displays inducing apparent self-motion perception, with an increase in parieto-occipital areas in the occipital cortex with a simultaneous decrease in the PIVC bilaterally [4]. In theory, this relationship allows the dominant sensorial weight to be shifted from one modality to the other, depending on which mode of stimulation predominates [4].

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Chapter 2
Mechanism of Compensation After Unilateral Loss

Si Chen and Eric Wilkinson

Functional Changes in Vestibular Compensation

Vestibular compensation is a neurologic phenomenon of central nervous reorganization that allows functional recovery after a peripheral vestibular input loss. Three main mechanisms are responsible for vestibular compensation: adaptation, substitution, and habituation.

Adaptation is the change in central nervous system regulation of neuronal activities that enables reduced sensitivity and clinical response to a constant environment. After unilateral peripheral vestibular weakness, both static and dynamic deficiencies are created which must be overcome. Static deficiencies are due to a constant asymmetric firing rate of the vestibular nuclei. Presenting as acute rotary vertigo symptomatically and spontaneous nystagmus on exam, they often resolve over a short time period. Dynamic deficiencies occur with head movement and are manifested as changes in the vestibular-ocular reflex (VOR). The normal VOR moves the eye during head movement in order to stabilize visual targets onto the fovea. Normal gain in VOR is 1; meaning the amplitude and speed of eye movement are exactly the opposite of head movement. With vestibular loss, the gain is reduced; thus patients experience retinal slip which is interrupted as a visual disturbance. Adaptation to dynamic vestibular loss is seen when the gain of VOR increases over time to regain stable gaze and visual focus during head movement [9].

Substitution occurs with sensory, behavior, and cognitive changes. Multiple inputs contribute to one's sense of equilibrium: vestibular, visual, and proprioceptive inputs. When vestibular input is lost in a unilateral peripheral vestibular injury, the central nervous system gives more importance to sensory and proprioceptive inputs to reestablish equilibrium [18, 21]. This is known as sensory substitution.

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Through behavioral substitution, patients develop behaviors that improve gaze stability and dynamic visual acuity in the setting of abnormal VOR response to movement. These include saccadic eye movements and suppression of cortical visual motion processing [8, 28]. Other strategies are learned behavior such as closing the eyes during head movement to the lesion side, blinking with head movement, or moving the whole body as a block [23]. Cognitive substitution describes the phenomenon when the patient moves the whole trunk and head in anticipation of head movement [9].

Some methods in vestibular rehabilitation apply the concept of habituation to ameliorate clinical symptoms. Habituation differs from adaptation in that it is a progressive reduction in response with repetition of stimuli. In benign paroxysmal positional vertigo (BPPV) patients who underwent Epley's maneuver, additional vestibular rehabilitation has been shown to improve gait performance [6]. Rehabilitation with rotational movements in rotatory chair is also shown to reduce VOR gain discrepancies and treat visual disturbances [30]. With habituation, patients learn to tolerate or become desensitized to dizziness and vertigo.

All three mechanisms of vestibular compensation have complex interaction in the functional recovery of a patient. Each patient goes through a unique process of vestibular compensation with differential utilization of these mechanisms.

Structural Changes in Vestibular Compensation

In addition to functional changes, structural alterations in the central nervous system have been demonstrated in a series of elegant studies in the past decade. A cascade of molecular and cellular events can be seen from the brain stem to the cortex.

At the brain stem level, acute unilateral vestibular loss creates an asymmetric resting discharge of the vestibular nucleus complexes on both sides. The ipsilateral vestibular nucleus decreases the firing rate and sensitivity to inhibitory neurotransmitters. At the same time after vestibular injury, the contralateral vestibular nucleus increases its firing rate and increases inhibitory activity. With vestibular compensation, the ipsilateral firing rate returns to normal within a week; however, the sensitivity to head velocity does not return to normal [33, 35]. In the lesioned vestibular nuclei, animal studies demonstrate increased inflammatory markers, neuroprotective and neurotrophic factors, cellular metabolism, cell proliferation, and axonal growth [10, 19, 26, 32, 36].

The acute stress response is activated in acute vestibular loss [13]. Elevated cortisol and ACTH levels are seen in Meniere's and vestibular schwannoma patients [20]. In cat models of unilateral vestibular neurectomy, increase in stress hormone (vasopressin, corticotropin-releasing factor)-reactive cells is seen in paraventricular nucleus [37]. Stress hormones alter the milieu of neurotransmitters (glutamate, acetylcholine, GABA, glycine) and neuromodulators (histamine, adrenaline, noradrenaline). Clinically patients experience anxiety with acute vestibular loss, and poorly

compensated patients continue to suffer anxiety and depression [12]. Modulating neurotransmission with histaminergic ligands has been shown to improve vestibular compensation in cats. Neurochemical studies in vestibular compensation are an opportunity for pharmacological intervention to accelerate recovery.

New imaging modalities have improved our understanding of higher-level cortical changes with unilateral vestibular loss and subsequent vestibular compensation. Alterations in the cortical structure, cerebral metabolism, and functional connectivity contribute to vestibular compensation.

Functional MRI of vestibular neuritis patients demonstrated gray matter volume (GMV) changes in the superior temporal gyrus, insula, inferior parietal lobe, middle temporal areas, and posterior hippocampus. In particular, the increase in GMV of the contralateral superior temporal gyrus and posterior insula (ascending vestibular pathway) correlated with the level of functional impairment [14]. GMV increase in somatosensory and visual cortex (middle temporal areas) was also noted, which corroborates with clinical findings that patients rely on somatosensory and visual input when there is a loss of vestibular input [15]. In addition, the extent of functional recovery as measured by Dizziness Handicap Inventory also correlates with GMV increases in the visual cortex [17]. Together this imaging evidence suggests that vestibular compensation depends on the increased use of contralateral vestibular afferents and other sensory inputs in response to defective ipsilateral vestibular input.

Cerebral glucose metabolism is altered in animal models of unilateral labyrinthectomy (UL). FDG-microPET studies revealed asymmetric glucose metabolism in the vestibulocerebellum, thalamus, temporoparietal cortex, hippocampus, and amygdala following UL in rats [39]. With vestibular compensation, glucose metabolism is first re-balanced in the vestibular nuclei, thalami, and temporoparietal cortices within 1–2 days. Bilateral glucose metabolism increases in the hippocampus and amygdala and later in vestibulocerebellum and hypothalamus in 7–9 days [39]. These support the neuronal plasticity and contribution of thalamocortical and limbic areas to vestibular compensation. Human studies of acute and chronic peripheral vestibular loss using FDG-PET demonstrate an activation pattern similar to peripheral vestibular stimulation on the contralateral side in healthy subjects. There is an increase in glucose metabolism in the contralateral thalamus and vestibular cortex, which is reversed within 3 months after peripheral vestibular nerve lesion [2, 3].

Studies using fMRI revealed that functional interregional connectivity (resting-state activity) is altered with unilateral vestibular loss. Vestibular signals are conveyed to multiple cerebral regions via distinct pathways in healthy subjects. In the acute phase of vestibular neuronitis, there is decrease in functional connectivity in contralateral parietal lobe (intraparietal sulcus and supramarginal gyrus) in human subjects, which participates in spatial orientation and multisensory integration. With vestibular compensation, functional connectivity is increased over 3 months. In addition, patients with little disability demonstrate larger increase in functional connectivity on follow-up examination [16]. The changes in functional connectivity or resting-state activity reflect a shifting vestibular tone in cortical areas responsible for spatial perception and orientation that underlie the process of vestibular compensation.