Chapter 2
The Physiology of the Vestibular System

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Introduction

Human evolution has advanced through a variety of steps, of which one of the most significant has been the progress to bipedal locomotion and a vertical posture. This upright position, which allows walking and improves access to environmental awareness and vigilance, has been reached through an extremely delicate adaptation of a series of systems, which include arch reflexes and neurogenic modulation and harmonization encompassing the vestibular, ocular, proprioceptive, and central nervous systems.

In fact, body balance results from the multisensorial integration centered in the vestibular nuclei, which sends information to motor structures, including the cerebellum and spinal cord, which play an important role in postural dynamics and

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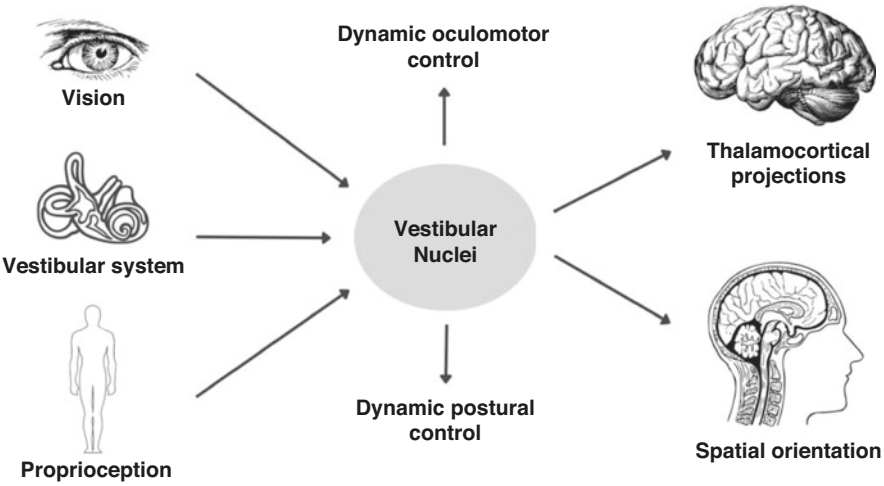

Fig. 2.1 Mechanisms involved in balance

oculomotor control. Also, ascending projections towards the cortex contribute to cognitive functions such as spatial orientation and memory [1–3] (Fig. 2.1).

Embryogenesis of the Inner Ear

Phylogenetics

The development of a vestibular organ dates back around 500 million years, with the development of the statocyst in species belonging to the *coelenterates phylum*, such as hydras or jellyfish [4]. In addition to the gravity detection mechanism, it is likely that the statocyst allowed the organism to respond to sound waves. Regarding the phylogenetic development of the labyrinth, the vestibular part developed first, while the cochlear organ appeared later [5].

The mammalian ear, in which the human ear is included, is divided into outer, middle, and inner ear. The ear components derive from neural crest cells and the three germ layers (ectoderm, mesoderm, and endoderm), and their embryologic development is associated with the first and second pharyngeal arches [6, 7]. The inner ear originates from the ectoderm and is the first part of the ear to develop.

Embryology

Around the fourth week of gestation, a thickening of the ectoderm, the otic placode, appears. It soon starts to invaginate the surrounding mesoderm, creating the otic pit [5, 7]. Fusion of the otic pit edges originates in the otic vesicle, or otocyst, the

precursor to the membranous labyrinth. Thus, the membranous labyrinth inner layer derives from the ectoderm, while the outer layer is of mesodermal origin [7, 8]. The otocyst has two distinct regions: a dorsal vestibular/utricular part, which will give rise to the utricle, semicircular canals (SCCs), and endolymphatic duct, and a ventral auditory/saccular part, from which the saccule and cochlear duct originate [7, 9]. The otic capsule formation begins with a process of chondrification of the mesenchyme around the otocyst that originates a cartilaginous otic capsule. Later, the cartilage is reabsorbed and replaced by bone [5, 7]. These structures will develop to form the well-known vestibular and cochlear organs and the corresponding sensory epithelium that comprises the *cristae* of the SCCs, the utricular and saccular *maculae*, and the organ of Corti. The development of the inner ear ends, and the labyrinth reaches its adult size and shape around the 20th to 22nd week of gestation [7].

Anatomy of the Bony and Membranous Labyrinth

The inner ear, or labyrinth, is enclosed within the petrous part of the temporal bone and contains the vestibulocochlear sensory organs [8]. It is composed of a series of hollow channels and cavities in the temporal bone—the bony labyrinth—inside which are located channels bounded by a membranous wall—the membranous labyrinth. The membranous labyrinth is composed of individual structures that are continuous with each other: the three SCCs, the utricle, the saccule, the cochlear duct, and the endolymphatic duct and sac [5]. The space between the bony labyrinth and the external surface of the membranous labyrinth is filled with perilymphatic fluid, while the membranous labyrinth contains endolymph. Globally, the inner ear has a posterior part, corresponding to the SCCs: a middle part, the vestibule (both associated with the vestibular function); and an anterior part, the cochlea, dedicated to the auditory function.

The SCCs are three bony tunnels with a corresponding membranous canal on the interior. According to their spatial orientation in the anatomical position, they are named the superior (or anterior), horizontal (or lateral), and posterior SCCs. Each one has two extremities, both opening to the vestibule. One of the extremities in each canal has a dilation corresponding to the *ampulla*, which contains the *crista ampullaris*, where lies the sensory epithelium of the SCCs. The non-ampullary ends of the posterior and superior canals join to form a common opening in the vestibule (*crus commune*).

The vestibule is a cavity with an oval shape, inside which reside the otolith organs, the utricle and saccule [8]. Each one consists of a membranous chamber filled with endolymph and containing a *macula* composed of sensory epithelium [5]. The medial wall of the vestibule lodges the utricle in a superior recess and the saccule in an inferior recess [10]. A narrow utricular canal and saccular canal emerge from the respective chambers and join in a common tunnel, forming the endolymphatic duct [8]. The endolymphatic duct (a component of the membranous labyrinth) runs inside the corresponding structure in the bony otic capsule, the vestibular

aqueduct. The endolymphatic duct end enlarges to form the endolymphatic sac that rests on the posterior surface of the petrous bone, enveloped in dura layers [11].

Anteriorly, the cochlea is a spiraled bony canal displayed in a conical shape, with 2½ to 2¾ turns around a central bony axis, the modiolus, in which the cochlear nerve and spiral ganglion are situated [12]. The membranous labyrinth part located inside the cochlea takes the name of the cochlear duct (*scala media*) and is filled with endolymph. A narrow canal, the *ductus reuniens*, connects the cochlear duct with the vestibule. Superior to the cochlear duct and separated from it by Reissner's membrane, lies the vestibular duct (*scala vestibuli*). The tympanic duct (*scala tympani*) is situated inferior to the cochlear duct and separated from it by the basilar membrane. Both vestibular and tympanic ducts contain perilymph and join each other at the cochlear apex—the helicotrema. The vestibular duct extends from the vestibule to the helicotrema, and the tympanic duct begins at the round window on the medial wall of the tympanic cavity.

How Do These Structures Interact?

In line with the previous section on anatomy, the current chapter will offer an integrated overview of the mechanisms, functions, and pathways of the vestibular system that, in brief, allow self-movement detection.

The main targets of this accurate system are to: (1) to ensure gaze stabilization; (2) enable balanced locomotion and body position; (3) provide general orientation of the body with respect to gravity; and (4) readjust autonomic functions after body reorientation.

As described, the *posterior pars* of the labyrinth is composed of the vestibule and SCCs. Inside the vestibule, two vesicles can be found: the saccule and utricle, which contain ciliated neuroepithelial cells aggregated in the macula and are covered with a gel topped with calcium carbonate otoconia (Fig. 2.2).

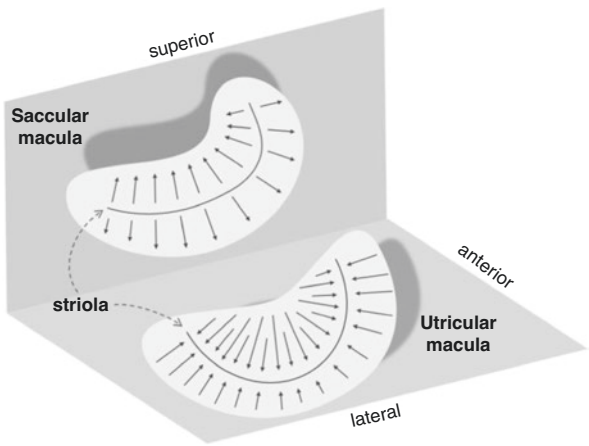

Fig. 2.2 Spatial orientation of utricle's and saccule's macula

In the upright position, the macula of the saccule stands vertically, and the macula of the utricle stands in the horizontal plane. These two structures, due to the specific weight and inertia of the otoconia, are essentially sensitive to forces of linear acceleration and gravity as a result of minute displacements of the otoconia. In contrast, the SCCs—superior, lateral, and posterior—are orthogonally disposed and have each one a terminal dilation or ampulla that lodges the ciliated neuroepithelial cells of the *crista ampullaris*, covered with a gelatinous cupula that stays inside the ampulla like a sail and moves forward or backward according to endolymph dynamics elicited by angular or rotational movements of the head (Fig. 2.3).

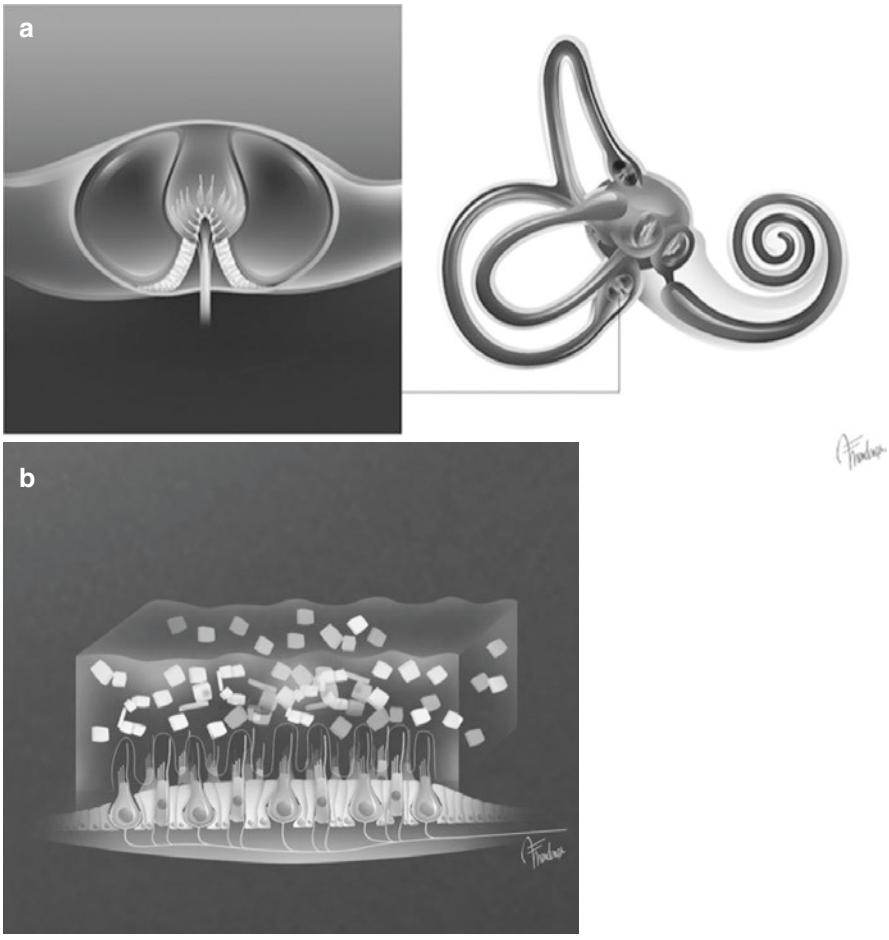

Fig. 2.3 (**a**) *Crista ampullaris* and (**b**) utricle (courtesy by Vilhena de Mendonça, MD - Círculo Médico)

The cupula, composed of mucopolysacharides produced by the support cells of the cristae, has the same density as the endolymph and therefore does not deflect with linear acceleration. However, rotational movements of the head, in any direction, at least stimulate the crista of one of the SCCs through the inertial movement of the endolymph that deflects the respective cupula. The movement of the endolymph inside the SCC is in the opposite direction from the head rotation. For instance, a head rotation to the right on the horizontal plane leads to a flow of endolymph towards the ampulla (ampullopetal), creating an excitatory stimulus to the crista of the right horizontal SCC and away from the ampulla (ampullofugal) on the left horizontal semicircular, leading to an inhibitory stimulus on this side. The function of the SCC complex was already postulated in 1892 by Ewald [13]

- Head and eye movements occur in the plane of the canal being stimulated and in the direction of the endolymph flow.
- In the horizontal canal, ampullopetal endolymph flow causes a greater response than ampullofugal flow.
- In the vertical canals, ampullofugal endolymph flow leads to a greater response than ampullopetal flow.

Each ciliated cell, either the more bottle-shaped type I (Fig. 2.4) or the more cylindrical type II (Fig. 2.5), shows at their apex one big cilium, or kinocilium, and a bundle of 60–100 smaller cilia, or stereocilia [14] (Fig. 2.6), distributed in a "pipe-organ" fashion and all connected by proteic myosin bundles [15].

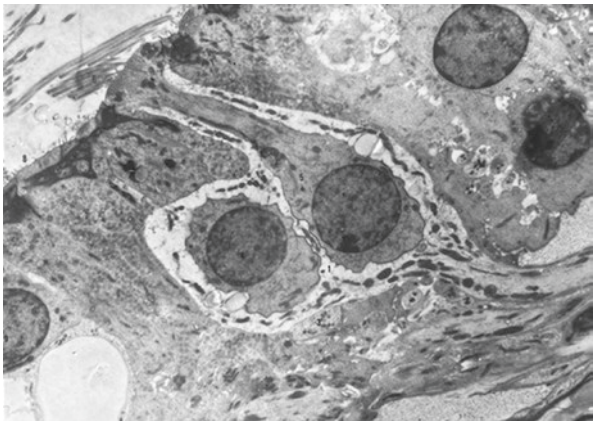

Fig. 2.4 Electron micrograph depicting two type I ciliated cells of the *crista ampullaris* of the lateral semicircular canal of the rat. Please note the flask-shaped form of the cell and the surrounding nervous calyx: (1) amyelinated calyx; (2) endpoint of the myelin sheet of the afferent nerve; (3) efferent synapsis; (4) type I cell nucleus; (5) Golgi apparatus; (6) cilia; (7) granules in support cell; (8) apical microvilli; and (9) nucleus of type II ciliated cell. (Courtesy of Jorge Spratley, MD, PhD)

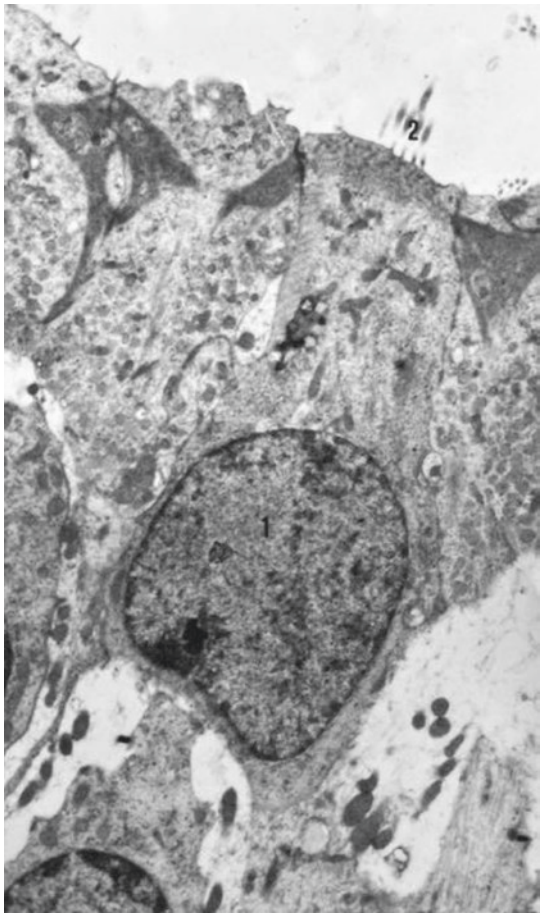

Fig. 2.5 Electron micrograph depicting a type II ciliated cell of the *crista ampullaris* of the lateral semicircular canal of the rat. Please note the cylindrical shape of the cell. (1) Nucleus and (2) Cilia. (Courtesy of Jorge Spratley, MD, PhD)

The movement of the stereocilia toward the kinocilium leads to a change in the permeability of the cell and its subsequent depolarization with the creation of a positive action potential (Fig. 2.7), which is transmitted to the nerve through the synapse at the cell base. The opposite movement—the stereocilia away from the kinocilium—in contrast, leads to the repolarization of the cell. These phenomena in the SCCs—depolarization on the right ear, repolarization on the left ear, and vice versa—occur simultaneously in a symmetrical fashion, leading to a precise perception of the central nervous system nuclei of the direction of the movement.

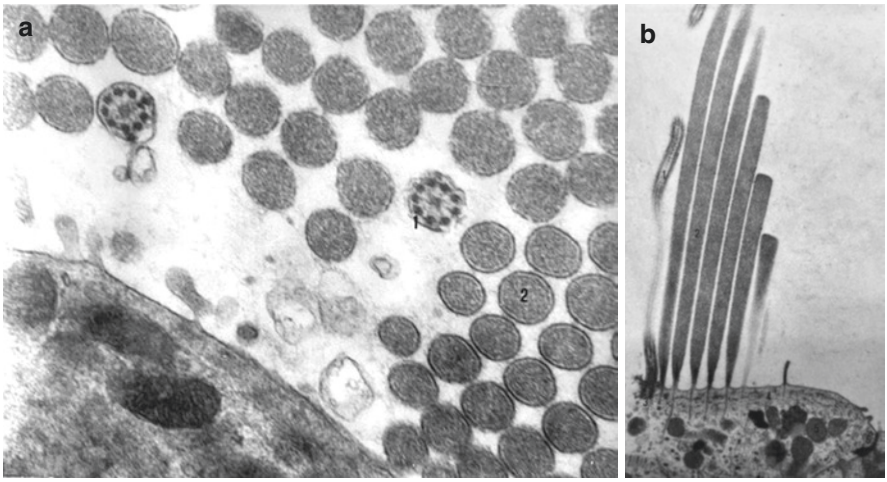

Fig. 2.6 (**a**) Electron micrograph depicting the cilia in a transversal section. (1) Kinocilium showing the typical array of nine pairs of microtubules. (2) Steriocilium, composed by an amorphous matrix of actin. (Courtesy of Jorge Spratley, MD, PhD). (**b**) Electron micrograph depicting the cilia in a longitudinal section. (1) Kinocilium; (2) steriocilia; (3) cuticular plate; and (4) union complex. (Courtesy of Jorge Spratley, MD, PhD)

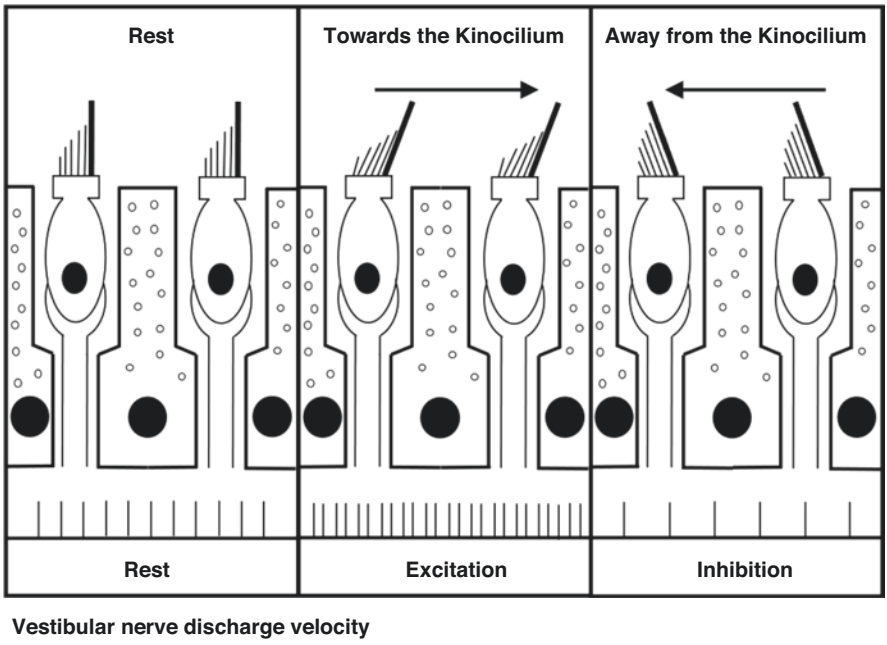

Fig. 2.7 Signal transduction in the vestibular system

Vestibular–Ocular Reflex

The vestibular–ocular reflex (VOR) is a response that permits the ocular fovea to remain on a target while the head moves. It actually allows the individual to recognize faces or read while moving, such as while walking or, even, after high-frequency head movements. It essentially responds to head accelerations, which can reach up to several thousands of degrees per square second. When sustained velocity is reached, the acceleration is no longer detected, and the stimulation is suspended after a few seconds as the cupula repositions itself in its central position.

This is possible because there is a response of the extrinsic muscles of the eye, when functioning properly, which leads the eye to move in the opposite direction of the head while keeping the same velocity and amplitude. If this system is not working properly and accurately, either due to a velocity or amplitude deficiency, the shift in gaze causes a retinal slip that is perceived as an image movement, designated by oscillopsia.

The information needed for these compensatory eye movements makes use of inputs from:

- SCCs and the otholits (VOR)
- Retina (optokinetic reflex)
- Neck somatosensors (cervico-ocular reflex)

These different loops provide convergent and redundant information ("functional overlapping"), a partial compensation for each other's deficiencies ("functional substitution"), and preferred frequency ranges of action ("functional specialization") [16].

The pathways involved are complex and encompass neuronal information transmitted from the vestibular system, with an increased weight in the SCCs, to the oculomotor muscles.

A classical three-neuron vestibular reflex pathway originates in the vestibular end organs, where fine-tuned motion sensors generate and transmit signals to the first-order bipolar vestibular ganglion cells, whose axons transmit signals to the vestibular nuclei neurons, which are then spread in the brainstem. Second-order vestibular nuclei neurons participating in the reflex pathways signal third-order, cranial, and spinal motor neurons, which control gaze, posture, and balance. Altogether, there are three major vestibular reflex pathways that regulate eye movements and balance essentially without involving cortical structures [17, 18].

Predictably, as it is actually easier to understand, we will illustrate how information is essentially conducted on the plane of the horizontal SCC (Fig. 2.8) [19]. The same occurs in the other planes, but due to the stimulation of different oculomotor muscles, the ocular movements are more complex. Indeed, there are three types of rotationally induced eye movements to be considered: horizontal, vertical, and torsional. Each of the six pairs of oculomotor muscles has to be coordinated to produce the desired response. The vertical SCCs and the saccule are sensible for controlling vertical eye movements, whereas the horizontal canals and the utricle regulate

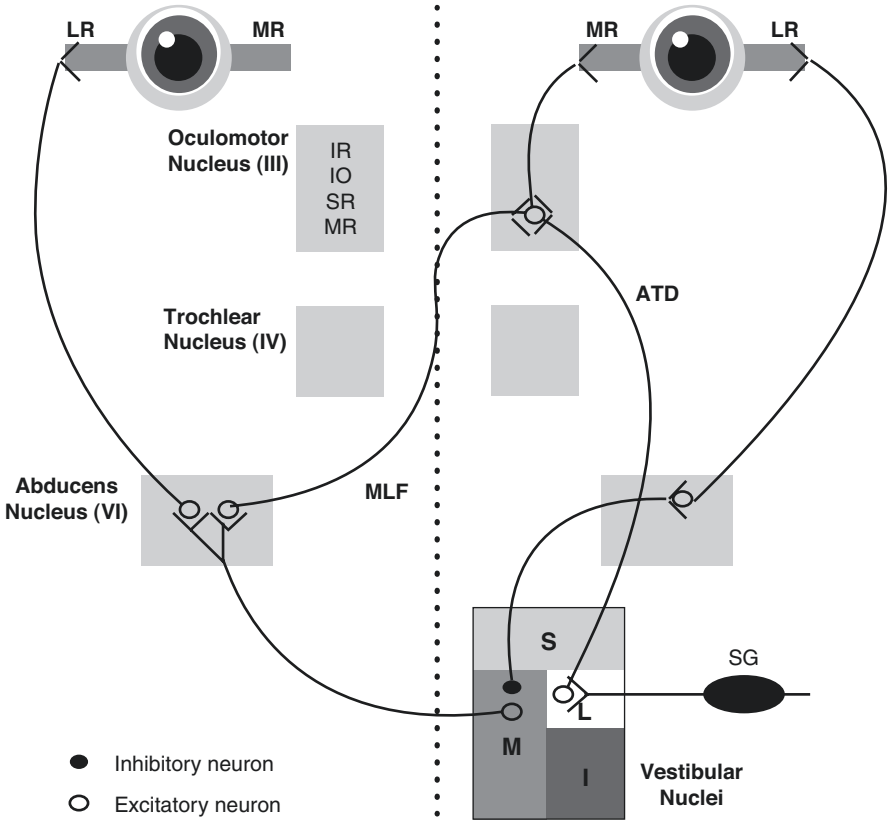

Fig. 2.8 Direct pathways of the horizontal semicircular canal vestibular–ocular reflex (adapted from Baloh 2001 [20]). *SC* scarpa ganglion, *S* superior nucleus, *L* lateral nucleus, *M* medial nucleus, *I* inferior nucleus, *MLF* medial longitudinal fasciculus, *ASD* ascending tract of Deiters, *IR* inferior rectus, *IO* inferior oblique, *SR* superior rectus, *MR* medial rectus, *LR* lateral rectus

horizontal eye movements. Torsional eye movements are essentially controlled by the vertical SCCs as well as by the utricle (Table 2.1).

The first afferent neuron synapsis is in the respective vestibular nuclei associated with a particular SCC (Table 2.1). In the specific case of the lateral SCC, this occurs in the lateral vestibular nuclei.

Specifically, when the head turns (accelerates) to the right (clockwise), on the precise plane of the horizontal SCC (Fig. 2.9), an ampullopetal endolymphatic flow occurs on the right side and an ampuloffugal flow on the left. As acknowledged, this action originates a deflection of the cupula and the cilia in the *crista ampullaris* of the right SCC towards the kinocilium and, consequently, the opening of mechano-sensory K^+ and voltage-gated Ca^{2+} channels, initiating an influx of both these ions into the cell with a subsequent depolarization. The previously described spontaneous basal activity of these sensory organs at rest also allows a status of hyperpolarization and inhibition on the left side, as the exact opposite motion occurs as a

Table 2.1 Vestibular organs and oculomotor Ipsilateral and contralateral activation

Vestibular organ	Vestibular nucleus	Ipsilateral oculomotor muscle	Contralateral oculomotor muscle	Ocular motion
Anterior SCC	Superior	Superior *rectus*	Superior *obliquus*	Upward and contradirectional torsional
Lateral SCC	Medial	Medial *rectus*	Lateral *rectus*	Conjugate deviation of the eyes to the opposite side
Posterior SCC	Medial	Superior *obliquus*	Inferior *rectus*	Downward and contradirectional torsional
Utricle	Lateral	Interstitial nucleus of Cajal and from there to the oculomotor and trochlear nuclei		
Saccule	Lateral	Vestibulospinal pathways		

SCC semicircular canal

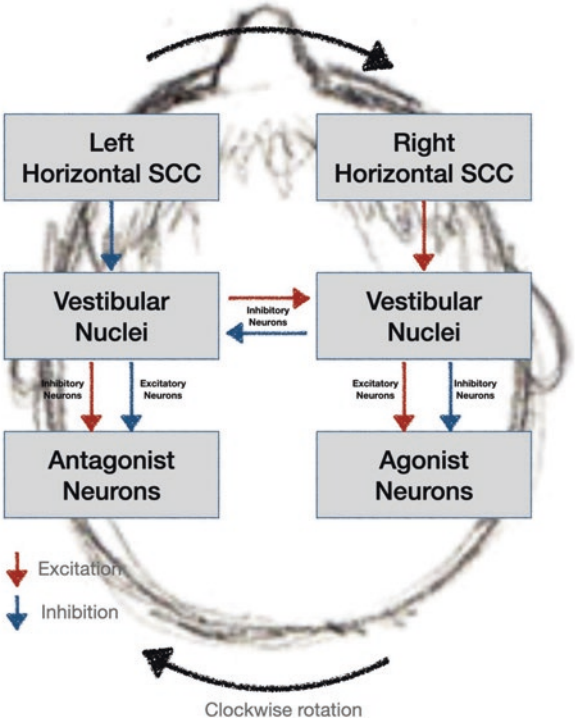

Fig. 2.9 Horizontal vestibular-–ocular reflex neuronal's drift overview

consequence of the reverse orientation of the cilia in the *crista ampullaris* on this side. During physiological rotatory stimulation, it has been revealed that the change in frequency of action potentials is roughly proportional to the deviation of the cupula [21].

This asymmetric information reaches the vestibular nuclei in the brainstem, mainly in the medial vestibular nuclei, where different connections mediate the VOR from the SCC to the oculomotor muscles (Fig. 2.9). In the situation presented, the vestibular nuclei interpret the discharge rates' difference between left and right SCCs as movement to the right and therefore trigger the oculomotor nuclei to drive the eyes to the left to maintain gaze.

The eye response to a head rotation resides in a slow phase until the eye reaches the edge of the outer canthus and a fast phase as a reset to the initial position. This pattern repeats itself as long as the stimulus continues, and these two types of repeated movements, as a saw-tooth pattern, characterize the vestibular nystagmus variety. The direction of the nystagmus is denominated by the fast phase, as it is the easiest to perceive. These movements can also be identified and characterized by vestibular testing procedures such as conventional videonystagmography.

Vestibulo-spinal and Vestibulo-colic Reflexes

While the extraocular muscles are responsible for the compensatory ocular response to movement, through the VOR, the extensor muscles of the neck, trunk, and limbs are accountable for the body response through the vestibulo-colic and vestibulo-spinal reflexes.

These reflexes trigger automatic compensatory movement of the head/trunk in very much the same way as with the VOR, controlling and balancing the extensor and flexor muscle tonus. These operate in coordination to achieve an appropriate balance, either in static or dynamic conditions. Gravity, as detected by the otolith system, acts as an additional driving input. Furthermore, proprioceptive and visual information concur to provide the correct body position, as gravity is only detected in the head, regardless of the position of the trunk and lower body.

Two functional categories of vestibulo-spinal reflexes can be distinguished: those acting on the limb muscles, which stabilize the position of the trunk in space, and those acting on the neck muscles (vestibulo-colic reflexes), which stabilize the position of the head in space [22].

The two most important vestibular descending pathways involve the lateral vestibulo-spinal tract (LVST) and the medial vestibulo-spinal tract (MVST). Reflexive control of head and neck muscles arises through the neurons in the MVST. These neurons comprise the rapid vestibulo-colic reflex, whose role is to stabilize the head in space and to participate in gaze control [23]. Yet, the MVST neurons receive input from both the vestibule and the cerebellum, as well as somatosensory information from the spinal cord. These neurons carry both excitatory and inhibitory signals to innervate neck flexor and extensor motor neurons in the spinal

cord, which clinically may be detected by the cervical vestibular evoked myogenic potentials (cVEMP).

Last but not least, the LVST receives input from the cerebellum, the vestibule, and the proprioceptive sensors of the spinal cord. These same LVST fibers project ipsilaterally to many levels of motor neurons in the spinal cord to ultimately provide coordination of different muscle groups for postural control [24].

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