Chapter 141: Anatomy of Vestibular End Organs and Neural Pathways

Anna Lysakowski, Robert A. McCrea, R. David Tomlinson

The vestibular system is the system of balance. In simple terms it consists of five distinct end organs: three semicircular canals that are sensitive to angular accelerations (head rotations) and two otoliths that are sensitive to linear (or straight line) accelerations. Although a great deal has been written about the function of these structures and a detailed description of that function is certainly not appropriate for a chapter such as this, certain basic points should be made because they will be of relevance to the more detailed description of anatomy that follows.

The semicircular canals are arranged as a set of three mutually orthogonal sensors; that is, each canal is at right angles (at least approximately) to the other two in the set much the way the three sides of a box that meet at each corner are at right angles to one another. Further, each canal is maximally sensitive to rotations that lie in the plane of that canal. The result of this arrangement is that the three canals can uniquely specify the direction and amplitude of any arbitrary head rotation. Each of the canals act as an integrating accelerometer; thus the necessary stimulus for the canal is an angular acceleration, but the information that is encoded by the firing of the afferent nerve fiber is more closely related to angular velocity. Finally, the canals are organized into functional pairs wherein both members of the pair lie in the same plane. Any rotation in that plane will be excitatory to one of the members of the paior and inhibitory to the other. Although in the horizontal system the two horizontal canals form a functional pair, the situation is somewhat more complex in the vertical system. Here, the anterior canal on one side is parallel and thus coplanar with the posterior canal on the opposite side. For example, the right anterior canal and the left posterior canal form a functional pair.

Since the primary afferent fibers exhibit a substantial resting firing rate, each canal is able to report rotations in either its excitatory direction (by increasing its firing rate) or its inhibitory direction (by decreasing). This observation explains why it is possible to function reasonably well after the loss of one labyrinth.

The vestibular system forms the basis for a number of rather fundamental reflexes: the vestibulocollic reflex (head stabilization), reflex control of upright posture, and the vestibuloocular reflex (retinal image stabilization). The last of these, the vestibuloocular reflex (VOR), has been studied far more than the others and is certainly the best understood; it is this reflex that forms the basis for most clinical testing (calorics, rotation tests, and so on).

This chapter describes the anatomy of the VOR in reasonable detail but without exploring every possible aspect. Many of the details that will be described have been obtained from experiments in animal species, principally the cat and monkey; nevertheless, the information is certainly applicable to humans, since the vestibular system has changed very little since the evolution of vertebrates.

Vestibular End Organs

Embryology of vestibular apparatus

The development of the inner ear is a complex process that starts at the beginning of the fourth week and is completed at about 25 weeks. By that time the vestibular apparatus has achieved adult form and size. What follows is a brief description of the process of development. Further deatils can be found by consulting more detailed references (Anson, 1973; O'Rahilly, 1963; Wright, 1987).

When the human embryo reaches the seven somite stage (about 22 days), surface ectoderm overlying the future site of the inner ear (at about the level of the first occipital somite) thickens to form the *otic placode.* The otic placode invaginates into the mesenchyme, forming an otic pit. At about 30 days the otic pit becomes pinched off, forming the *otic vesicle* or *otocyst* (Fig. 141-1). Concurrently at about 4 weeks, a portion of the neural crest migrates to the vicinity of the otic vesicle and becomes the acousticofacial ganglion. Soon the geniculate ganglion migrates away from this cluster of neurons, leaving the vestibulocochlear ganglion in close proximity to the otic vesicle.

Within 1 or 2 days after formation of the otic vesicle, its more medial portion, the *endolymphatic diverticulum,* becomes distinguishable from the lateral *utriculosaccular chamber*. This chamber differentiates by a constriction of its middle into (1) an utricular chamber that will give rise to the *utriculus* and the *semicircular ducts* and (2) a saccular chamber that gives rise to the *sacculus* and the *cochlea.* The utricular chamber differentiates first by a rapid expansion into three diverticula. At about 35 days the centers of these diverticula fuse together and break down, leaving spaces around the perimeter that become the three semicircular ducts. The superior semicircular duct forms first, at about 6 weeks, with the posterior and lateral ducts forming soon afterward in that order. Dilatations of one end of each of the semicircular ducts become the ampullae. The ampullar ends and the opposite ends of the ducts remain connected to the utriculus.

The saccual chamber differentiates by expansion and coiling of the cochlear duct. This duct becomes separated from the sacculus by a narrowing of the duct at its dorsal end to form the *ductus reuniens.* While morphogenesis proceeds within the otocyst, histogenesis of the sensory epithelium is also occurring. The arrival of afferent endings in the epithelium precedes hair call differentiation (Sans and Deschesne, 1985, 1987). In the third week a common macula, or specialized neuroepithelium, appears. Its upper part will become the utricular macula and cristae ampullares of the superior and lateral semicircular ducts, and its lower part becomes the saccular macula and crista ampullaris of the posterior semicircular duct. At 9 weeks the hair cells in the vestibular end organs are well differentiated and they exhibit typical synapses with nerve endings. The maculae reach adult form at about 14 to 16 weeks, the cristae at about 23 weeks, adn the organ of Corti at about 25 weeks. The mesoderm surrounding the membranous labyrinth becomes the bony otic capsule, or *bony labyrinth.* The membranous labyrinth is suspended in fluid (perilymph) within the bony labyrinth by a loose connective tissue termed *periotic tissue.*

Overall organization of labyrinth: relation to skull and cochlea

The vestibular apparatus is enclosed within a bony labyrinth, the vestibule, in the petrous portion of the temporal bone. The vestibular end organs include three semicircular canals, each oriented in a different plane, and two maculae, one roughly in the horizontal plane (the utriculus) and one in the vertical plane (the sacculus). There are two vertical semicircular canals, the anterior (also known as the superior) and posterior canals, and one horizontal (also known as the lateral) canal. The vertical canals are oriented roughly at 45 degrees in relation to the sagittal plane, and the horizontal canal is tilted upward about 30 degrees anteriorly from the horizontal plane (Fig. 141-2). The five vestibular end organs, along with the cochlea, are contained within an endolymph-filled membranous labyrinth (the endolymphatic space), which is itself contained in the perilymph-filled bony labyrinth (the perilymphatic space) (Fig. 141-3).

The vestibule is situated between the internal auditory meatus anteromedially and the middle ear cavity laterally (Fig. 141-4). The entrance to the mastoid antrum (the *aditus ad antrum*) is just lateral to the horizontal semicircular canal. The cochlea sits anterior to the vestibule and is connected to the vestibule by the narrow ductus reuniens (Fig. 141-3). Posterior and lateral to the vestibule are the mastoid air cells. Directly medial is the posterior cranial fossa, into which the endolymphatic duct and sac extend beneath the dura.

The seventh (facial and intermediate) and eighth (vestibulocochlear) cranial nerves emerge from the brain stem laterally at the cerebellopontine angle. They enter the vestibule and cochlea from the internal auditory meatus (Fig. 141-5), located medial to a point midway between the cochlea and vestibule. The facial nerve lies anterior and dorsal to the vestibulocochlear nerve. The two nerves separate just inside the meatus, and the facial and intermediate nerves continue laterally in their own canal, past the vestibule. Once past the vestibule, the facial nerve makes a 90-degree turn inferiorly to exit the temporal bone through the stylomastoid foramen. The vestibulocochlear nerve splits into a vestibular division, which turns posteriorly to supply the vestibule, and a cochlear division, which turns anteriorly to supply the cochlea.

The vestibular (Scarpa's) ganglion sits at the bottom of the internal auditory meatus. It has two parts, the superior vestibular ganglion and the inferior vestibular ganglion. Large ganglion cells in the superior and inferior ganglia provide afferent innervation to the central regions of the cristae and maculae, and small ganglion cells innervate the peripheral regions of these end organs (more on the regional specialization within the end organs below). There is a nerve branch associated with each ganglion. The superior (or anterior) vestibular nerve supplies the anterior and horizontal cristae and the utricular macula. The inferior (or posterior) vestibular nerve supplies the posterior canal and saccular macula. There are also a few small branches that anastomose between the larger divisions of the eight nerve. One such small branch is Voit's anastomosis, which runs from the superior vestibular nerve to the anterosuperior part of the sacculus. Another is the vestibulocochlear (Oort's) anastomosis, which runs from the inferior vestibular nerve to the cochlear nerve and carries cochlear efferents (see below). In addition, some intermediate nerve fibers cross to the vestibular nerve proximal to the superior vestibular ganglion and others corss back to the intermediate nerve distal to Scarpa's ganglion. It has been suggested (Chouard, 1975) that this fracial-vestibular anastomosis carries parasympathetic innervation to the vestibular labyrinth (for details on

these and other small fiber connections, see Lindemann (1969)).

Efferent innervation of peripheral vestibular apparatus

The efferent supply to the vestibular end organs arises from a small group of about 200 neurons lateral to the abducens nucleus and the genu of the facial nerve (Goldberg and Fernandez, 1980). These neurons project both ipsilaterally and contralaterally (Fig. 141-6). The contralateral pathway crosses the midline at the level of the facial genu and joins the ipsilateral pathway; then both pass ventral to the vestibular nucleus. At this point they are joined by cochlear efferents originating from the superior olivary complex (the olivocochlear bundle). All of the efferents then enter the vestibular nerve, coursing through the middle of the nerve in a small distinct bundle. At the end organs, these relatively few fibers branch profusely to innervate the entire sensory epithelium. They terminate as highly vesiculated boutons, making synaptic contacts with hair cells and afferent fibers (Engström et al, 1972).

Autonomic supply of peripheral vestibular apparatus

Postganglionic sympathetic fibers from neurons in the superior cervical ganglion also innervate the vestibular end organs. They are of two types: perivascular and nonvascular. The nonvascular sympathetic fibers run among the myelinated afferent fibers. The terminals of these nonvascular sympathetic fibers are found as free endings near the cells of Scarpa's ganglion, distal to the ganglion and underneath the sensory epithelium. They do not appear to penetrate the basement membrane into the sensory epithelium and so do not appear to have a direct effect on the hair cells or afferent fibers (Hozawa and Kimura, 1989). Their functional role remains unexplored, along with the functional role of any parasympathetic innervation of the vestibular sensory epithelium.

Inner Ear Fluids: Source and Composition

Endolymph

Among the extracellular fluids of the body, endolymph has a unique ionic composition. It has a low Na+ content (15 to 25 mM/L) and a high K+ content (Anniko and Wroblewski, 1986; Smith et al, 1954), causing it to resemble intracellular, rather than extracellular, fluid. It is generally agreed that the endolymph of the cochlea is produced by the marginal cells of the stria vascularis as a derivative of perilymph (Sterkers, 1985). Ultrastructurally, these cells have several of the morphologic properties of secretory cells: deeply invaginated nuclei (indicating a cell actively engaged in production and secretion), many microvilli on their apical surface, a large number of free ribosomes and many vesicles (again indicating active production and packaging of secretory products), deep infoldings on their basal surface containing many mitochondria, and long, thin cytoplasmic extensions. Presumably, the mitochondria provide the fuel for the energy-consuming process that pumps the endolymph out of the cell. By analogy, the so-called "dark cells" of the cristae and maculae (Kimura, 1969), which are separated from the neuroepithelium by a transitional zone, have similar ultrastructural characteristics. The stria vascularis of the cochlea and dark cells of the vestibular apparatus also have the biochemical properties of secretory cells. The stria vascularis has a high concentration of Na+/K+ ATPase, adenylate cyclase, and carbonic anhydrase, enzymes associated with active ion pumps and fluid transport. These enzymes have

also been demonstrated biochemically (Thalmann, 1971) and immunohistochemically (Spicer et al, 1990) in the dark cells of the vestibular apparatus. For reviews of the biochemistry of endolymph production, see the works by Feldman (1981) and Sterkers (1985).

The site of absorption of endolymph is presumed to be the endolymphatic sac, which is connected to the utriculus and sacculus by means of the endolymphatic duct and the utricular and saccular ducts. Morphologically, the columnar cells located here are specialized for absorption. Like intestinal cells, they have long microvilli on their luminal surface and contain many pinocytic vesicles and vacuoles. Experimental blockage of the endolymphatic duct produces endolymphatic hydrops, further suggesting that the endolymphatic sac is the normal site of absorption (Kimura, 1967).

Perilymph

The site of perilymph production is still controversial. It is unclear whether perilymp is derived as an ultrafiltrate of bloor or from cerebrospinal fluid (CSF) or from both. CSF can reach the vestibule by means of the vestibular aqueduct or by means of perivascular and perineural channels. There is more convincing evidence in favor of perilymph originating as an ultrafiltrate from blood. In terms of chemical composition, the amino acid content of perilymph, particularly glycine and alanine, is low compared with blood but much higher than CSF (Medina and Drescher, 1981). Also, changes in blood composition are reflected much more rapidly in perilymph than in CSF (Schneider, 1974), Kellerhals (1979) has proposed a dual origin of perilymph. He found that the majority (78%) was derived from blood and the remainder (22%) from CSF, based on experimental evidence involving removal of one or the other or both sources. Supportive evidence is given by a protein analysis study of perilymph (Schiebe and Haupt, 1985) that showed perilymph to be different from blood plasma and CSF. Perilymph leaves the ear by drainage through venules and through the middle ear mucosa.

Blood supply to vestibular end organs

The main blood supply to the vestibular end organs is through the internal auditory (labyrinthine) artery, which arises most often (45%) from the anterior cerebellar artery, superior cerebellar artery (24%), or basilar artery (16%), according to a radiographic study by Wende et al (1975). Shortly after entering the inner ear, the labyrinthine artery divides into two branches: the anterior vestibular artery and the common cochlear artery (Fig. 141-7). The anterior vestibular artery provides the blood supply to most of the utriculus and the superior and horizontal ampullae, as well as some blood to a small portion of the sacculus. The common cochlear artery forms two divisions, the proper cochlear (or spiral modiolar) artery and the vestibulocochlear artery. The latter then divides into a cochlear ramus and a vestibular ramus, also known as the posterior vestibular artery. The posterior vestibular artery is the source of the blood supply to the posterior ampulla, the major part of the sacculus, and parts of the body of the utriculus and horizontal and superior ampullae.

Anatomy of End Organs

At the dilated end of each semicircular duct is the the ampulla. It contains the neuroepithelium (crista ampullaris), the cupula, supporting cells, connective tissue, blood vessels, and nerve fibers. The crista is a saddle-shaped, raised section of the wall that extends across the floor of the ampulla at right angles to its long axis. The crista has been found to be divided into central (near the apex) and peripheral (on the slope) zones based on the morphology and physiology of vestibular afferents supplying the different regions (see more below and Fig. 141-11). The shape of the crista facilitates maximal packing of specialized mechanoreceptor hair cells. Both the hair cells and the supporting cells are modified columnar epithelial cells that have microvilli on their apical surfaces. In the hair cells, many of these microvilli are elongated to form stereocilia, which are grouped in an organ pipe-like arrangement (Figs. 141-8 and 141-9). In addition, each hair cell has a single long kinocilium, a true cilium demonstrating the 9+2 arrangement of microtubules. This kinocilium is longer than the stereocilia and eccentrically located, imparting a certain polarization to the hair cell that has important functional implications. Displacement of the "hair (or stereociliar) bundle" toward the kinocilium results in an increase in the firing rate of the afferent fiber(s) contacting the hair cell. Displacement of the hair bundle away from the kinocilium results in a decrease in firing rate (Fig. 141-9) (Lowenstein and Wersäll, 1959). In the cristae the kinocilium on each hair cell is located on one end of the cell (Fig. 141-10). In the horizontal crista the kinocilia are located on the side of the hair cell that is closest to the utriculus. In the vertical cristae the kinocilia are located on the side of the hair cell furthest from the utriculus, the canalicular side. The entire hair bundle extends upward into the cupula (Fig. 141-11, A).

The cupula is a gelatinous mass (mucopolysaccharides within a keratin meshwork) (Dohlmann, 1971) that extends from the surface of the cristae to the roof and lateral walls of the membranous labyrinth, forming a fluid-tight partition. There is a distinct subcupular space in the region of the cupula overlying the apex of the center of the crista (Fig. 141-11). This subcupular space is believed to provide space for freedom of movement and more sensitive responses to endolymph flow for the stereocilia on the hair cells in the central zone. The specific gravity of the cupula is approximately 1.0, which is about the same as that of endolymph (Money et al, 1971). This matching of the specific gravity of the cupula and the endolymph is necessary to prevent the cupula from "floating up" in certain head positions and causing an enduring nystagmus. Disruption of this match in specific gravity is likely the cause of postalcoholic nystagmus.

A torsion pendulum model is used to describe the mechanics of cupular and endolymph displacement (Steinhausen, 1933). For a description of the mathematic details of the response of canal afferents, see Goldberg and Fernandez, 1984).

As mentioned previously, during most natural head movements, the hair cells behave as if the system were a velocity transducer. Outside of the middle frequency range (approximately 0.1 to 2 Hz), however, two deviations from this model occur. The first involves sensory adaptation, which causes a decline in afferent responses to rotational stimuli at very low frequencies or during sustained constant acceleration rotations. The second is a gain (or sensitivity) increase to values above those predicted by the model that is seen at frequencies greater than 2 Hz.

Like the cristae ampullares, the maculae of the utriculus and sacculus consist of neuroepithelium, supporting cells, blood vessels, and nerve fibers. The utricular macula is oriented in the horizontal plane, and the saccular macula is oriented in the vertical plane (Fig. 141-12). Cilia from the hair cells in both maculae extend upward into their respective *otolithic membranes* (Fig. 141-13), gelatinous membranes somewhat analogous to the cupula. In the upper surface of the otolithic membranes, the otoliths (or otoconia) are embedded. Otoliths are inorganic crystalline deposits composed of calcium carbonate or calcite (Ross et al, 1985). They vary in size from 0.5 to 30 microm, with most being about 5 to 7 microm (Lindemann, 1969). The specific gravity of the otolithic membrane is much higher than that of the endolymph, about 2.71 to 2.94 (Money et al, 1971). Within the otolithic membrane is the *striola* (Werner, 1933), a specialized central region that has a snowdriftlike appearance. The striola is identifiable as a thin stripe running down the center of the otolith membranes of both maculae. In the striola the otoliths are very small (about 1 microm) and the thickness of the otolithic membranes is either reduced, as in the utricular macula, or increased, as in the saccular macula. These regional differences in the otolithic membranes are paralleled by morphologic and physiologic differences in the afferent fibers supplying the hair cells in the underlying sensory epithelium.

The kinocilia on the hair cells in the maculae are also dynamically polarized, but the pattern of polarization is much more complex than in the cristae (Figs. 141-10 and 141-12). In the utricular macula, the kinocilia are oriented so that they point toward the striola, whereas in the saccular macula, the kinocilia point away from the striola. However, since both maculae are curved areas and the striolae therefore are curved lines, the arrangement is so complex (Fig. 141-12) that static head tilts in any direction cause some hair cells to be excited and others to be inhibited in one or both of the otolithic organs. Thus the stimulus is encoded by means of stimulation of hair cells in the appropriate sector of the macula. The otolith organs are sensitive not only to gravity but also to other linear acceleration forces, such as forward motion and bobbing movements of the head during walking. Thus static head tilts are represented by a vector and the afferent response predicted by a trigonometric function based on the tilt angle. One would expect a linear model based on this simple relation; however, there is a response asymmetry in that the excitatory response is somewhat larger than the inhibitory response. As a consequence, the equation describing this force-response relation is by necessity nonlinear (for more mathematical details, consult the series of papers by Fernandez and Goldberg (1976a, 1976b)).

Cellular Morphology of Vestibular Sensory Epithelium

The sensory epithelium is made up of several different elements: hair cells, supporting cells, afferent nerve fibers and their synaptic terminals, and efferent nerve fibers and their synaptic boutons.

Two basic cell types are present within the sensory epithelium: supporting cells and hair cells (Fig. 141-14). Supporting cells extend from the basement membrane to the apical surface. Their nuclei are usually found just above the basement membrane and below the hair cells. In sections taken tangential to the apical surface, several supporting cells can be seen to form a ring around an individual hair cell. The supporting cells themselves contain well-developed Golgi complexes, many mitochondria, and occasional lipid droplets. The upper part of the supporting cells contains large numbers of round or ovoid granules (Engstrom et al,

1972). The function of these secretory granules is uncertain, but it is conceivable that they may be responsible for the formation of the cupula and otolithic membrane.

Hair cells, in general, contain a bundle of stereocilia attached to their apical surface and grouped in a staircase arrangement. These stereocilia are densely packed with longitudinally oriented actin filaments that extend into the hair cell and are anchored in a thickened region near the apical surface, termed the *cuticular plate.* The cuticular plate is a dense filamentous meshwork of randomly oriented actin filaments that fills up the area just under the apical surface of the cell, except for the region of the kinocilium. In the region of the kinocilium, there are usually a basal body and many large vesicles. Hair cells are surrounded by supporting cells, as mentioned above, and form tight junctions and desmosomes with the supporting cells, thus separating the endolymphatic space, in which endolymph bathes the stereocilia above the cells, from the perilymphatic space below the apical surface. Another general feature that applies to hair cells is that they are presynaptic to the afferent nerve fibers that they contact. Hair cells make synaptic contacts by means of synaptic specializations termed *synaptic ribbons* or *bars,* electron-dense structures with synaptic vesicles clustered around them.

Synaptic Morphology of Vestibular Afferents

Hair cells are of two types, type I and type II, defined by the presence or absence of a *calyx,* or chalice, a specialized type of large afferent ending that completely surrounds the cell except for the near-apical and apical surfaces (Fig. 141-14). Type I hair cells are flask-shaped cells surrounded by a calyx ending. Usually, a calyx will surround a single type I hair cell. In this case the calyx ending is termed a *simple calyx ending.* Sometimes calyx endings are much more common in the central zone (or striola) than in the periphery (or extrastriola). In fact, histologically, the existence of complex endings is a criterion that can be used to define the central zone. It has long been assumed that the ratio of type I to type II hair cells is approximately 1:1 and that this ratio changes very little from the central to the peripheral zone, based on studies in which rodents have been used to quantify cell distributions (for example, Lindemann (1981)). Recent work, however, in the crista of the squirrel monkey has demonstrated that while the total number of hair cells is similar to rodents, the ratio of type I and type II hair cells in the central zone is increased from 1:1 to about 5:1 in primates as compared to rodents (Fernandez et al, 1991), possibly reflecting the relative importance of type I hair cells for primates.

Type II hair cells are cylinder-shaped cells that are contacted at their basal surfaces by numerous afferent and efferent synaptic boutons. Afferent boutons contain mitochondria and few vesicles and receive synaptic contacts from the hair cell. They transmit the impulse centrally to the vestibular nuclei and are postsynaptic to the hair cell. Efferent boutons contain many vesicles and smaller mitochondria and vesicles than those found in afferent boutons. They form synapses with hair cells and afferents, and transmit impulses from the efferent group of neurons located in the brain stem. They are presynaptic to hair cells. It has long been assumed that hair cells from different regions had approximately the same number of afferent boutons contacting them and that each bouton formed about the same number of synapses with a given hair cell. Recent ultrastructural work (Goldberg et al, 1992; Lysakowski and Goldberg, 1990) has shown that there are regional variations in the synaptic innervation of type II hair cells (Fig. 141-15). Type II hair cells in the periphery (or extrastriola) make

synaptic contact with many afferent boutons, each of which receives one synapse from the adjacent hair cell. Type II hair cells in the central zone (or striola) make synaptic contact with relatively few afferent boutons but make multiple contacts with each of these. In addition, type II hair cells in the central zone make synaptic contacts with the outer surface of the calyx endings surrounding type I hair cells, a type of synapse that is rarely found in the peripheral zone.

Synaptic Morphology and Function of Vestibular Afferents

Recent morphophysiologic work on vestibular afferents (Baird et al, 1988; Fernandez et al, 1988, 1990; Goldberg et al, 1990a, 1990b) has defined, both structurally and functionally, specialized subregions within the sensory epithelium (loosely analogous to the fovea and periphery of the retina): the central and peripheral zones of the vestibular sensory epithelium. These studies have involved experiments in which vestibular afferent nerve axons were impaled with microelectrodes, characterized electrophysiologically using responses to galvanic, rotational, and linear acceleration stimuli, and injected with horseradish peroxidase (HRP) used as an intracellular dye. The HRP-filled afferent nerve fibers were then recovered histologically, their position within the sensory epithelium reconstructed, and their nerve terminals and axons drawn. In this manner, these investigators were able to morphologically define three types of afferent endings: pure calyx (or chalice) endings, bouton endings, and dimorphic endings (which contained both calyx and bouton terminals) (Figs. 141-16 and 141-17); and to determine that the distribution of these three types was segregated within the sensory epithelium. In addition, these three morphologic types of afferents fell into two physiologic types that were also segregated within the sensory epithelium. Pure calyx endings had a very irregular discharge pattern and were fairly insensitive (low gain) in response to sinusiodal head rotation. Calyx endings were found only in the central region. Bouton and dimorphic endings were distributed along a continuum in which discharge regularity and response dynamics were linearly correlated; that is, bouton endings were very regularly discharging and had los sensitivity to sinusoidal head rotation, whereas dimorphic endings could vary from very regular to very irregular in discharge rate and from very low gain to very high gain response dynamics. Bouton endings were always found near the periphery. Dimorphic endings were found throughout the sensory epithelium, but irregular dimorphic endings were found in the central zone and regular dimorphic endings were in the peripheral zone.

Central Pathways of Vestibular System

Terminations of vestibular nerve in brain stem

The vestibular nerve enters the brain stem at the ventrolateral aspect of the pontomedullary junction in close proximity to the cochlear and facial nerves, which accompany it to the internal auditory meatus. After entering the brain stem, the fibers of the vestibular nerve course dorsally and medially, passing between the inferior cerebellar peduncle and the descending tract of the trigeminal nerve, and enter the vestibular nuclei. On entering the nuclei, a vestibular fiber typically gives rise to branches that course rostrally and caudally in the vestibular nuclei (Fig. 141-18). There are two major projection sites in the brain, the vestibular nuclei and the cerebellum. The cerebellar projections of the vestibular nerve appear to arise from collaterals of primary vestibular afferents that also terminate in the vestibular

nuclei.

Projections of vestibular nerve to cerebellum

Primary vestibular afferents terminate in the granular layer of the medial aspect of the cerebellar cortex (the cerebellar vermis) as mossy fibers and send collateral projections to the fastigial nucleus, which is the deep cerebellar nucleus that receives input from the vermis. The projection to the cerebellar cortex is primarily to the most caudal lobules of the vermis, a region of the cerebellum that is though to be involved in coordinating movements of the head and eyes. The Purkinje cells in the posterior vermis of the cerebellar cortex project to either the fastigial nucleus or the vestibular nuclei. Somewhat surprisingly, another region of the cerebellar cortex that projects directly to the vestibular nuclei, the cerebellar flocculus, does not appear to receive significant direct inputs from the vestibular nerve (Langer et al, 1985a).

Anatomic subdivisions of vestibular nuclei

The vestibular nuclei have been classically divided into four main regional subdivisions, the superior, medial, lateral, and inferior vestibular nuclei, and several minor cell groups (Fig. 141-19) (Brodal et al, 1962).

The superior vestibular nucleus is located dorsally and rostrally in the vestibular complex. It can be subdivided into a central region that contains many large- and medium-sized neurons and a peripheral region that contains mostly smaller cells. The superior vestibular nucleus is generally thought to be primarily involved in vestibuloocular reflex (VOR) pathways. Most of the neurons in this nucleus fire in relation to eye movements as well as head movements (Tomlinson and Robinson, 1984), and the most prominent efferent projection of this nucleus is to the oculomotor nucleus.

The lateral vestibular nucleus can be subdivided on anatomic and functional grounds into two subnuclei: the dorsal lateral vestibular nucleus (or Deiters' nucleus) and the ventral lateral vestibular nucleus. The dorsal lateral vestibular nucleus contains many large neurons that give rise to the lateral vestibulospinal tract, and the ventral lateral vestibular nucleus contains medium-sized neurons that give rise to vestibuloocular pathways, the medial vestibulospinal tract, and vestibulothalamic pathways. The two subdivisions of the lateral vestibular nucleus also differ in regard to their afferent inputs (see below).

The medial vestibular nucleus is the largest subdivision of the vestibular nuclei. It extends rostrocaudally in the brain stem from the level of the abducens nucleus to the hypoglossal nucleus. It is bounded medially by a functionally related nucleus, the nucleus prepositus, and laterally by the inferior vestibular nucleus. Functionally, the medial vestibular nucleus can be subdivided into rostral and caudal regions. The rostral medial vestibular nucleus, like the superior nucleus, contains many neurons whose firing behavior is related to eye movements and which project to the extraocular motor nuclei (Lisberger and Miles, 1980; McCrea et al, 1987a, 1987b). Little is known about the functions of the caudal medial vestibular nucleus, although many of the cells in this region appear to project to the cerebellum.

The inferior vestibular nucleus merges rostrally with the ventral lateral vestibular nucleus and is the most caudally extending nucleus in the vestibular complex. This region of the vestibular nuclei is one of the primary recipients of vestibular afferents that innervate the otolithic organs (Kevetter and Perachio, 1985). Some of the cells in this nucleus contribute to the vestibulospinal pathways, but the major projection from this area appears to be the cerebellum.

The minor cell groups associated with the vestibular nuclei have been named alphabetically: cell groups X, Y, Z, and E. Cell group Z is not properly included in the vestibular nuclei. It is located in the caudal part of the vestibular complex, it receives its priary input from fibers that travel in the spinal dorsal columns, and its cells contribute to ascending somatosensory pathways to the thalamus. Cell group X is also located in the caudal part of the vestibular complex. This area receives a prominent input from the spinal cord, and it projects to the cerebellum.

Cell groups Y and E are important functional subdivisions of the vestibular nuclei. The Y group is located caudal and lateral to the superior vestibular nucleus and is bounded dorsally by the lateral vestibular nucleus and ventrally by the inferior cerebellar peduncle. The dorsal and ventral parts of the Y group of cells appear to be functionally different. The ventral part of the Y group consists of small fusiform neurons that receive inputs from the vestibular afferents that innervate the sacculus (Kevetter and Perachio, 1985). The dorsal part of the Y group contains larger neurons and is traversed by a fiber tract that passes from the cerebellar flocculus to the vestibular nuclei, the floccular peduncle. Many of the cells in the dorsal part of the Y group appear to be functionally related to the flocculus and to eye movement control, particularly eye movements in the vertical plane (Chubb et al, 1984). Cell group E is located at the ventromedial aspect of the rostral medial vestibular nucleus, and it contains the cells that give rise to the efferent pathway from the brain to the vestibular end organs (Goldberg and Fernandez, 1980).

Organization of vestibular nerve inputs to vestibular nuclei

The vestibular nerve terminates in virtually all parts of the vestibular nuclei (Carleton and Carpenter, 1984). Although there are very few terminations of vestibular primary afferents in the dorsal lateral vestibular nucleus, electrophysiologic studies have shown that many of the cells in that part of the vestibular nuclei also receive monosynaptic inputs from the vestibular nerve (Boyle et al, 1992). The details of the terminations of the afferents that innervate individual vestibular end organs are not yet completely known, but cells whose activity is related primarily to otolith function have been found mainly in the dorsal lateral and inferior vestibular nuclei, whereas cells whose activity is primarily related to semicircular canal function have been found mainly in the superior, medial, and ventral lateral vestibular nuclei. Although the results of physiologic studies suggest that afferents that innervate different vestibular end organs do not synapse directly on the same cells in the vestibular nuclei (Wilson and Felpel, 1972), the activity of individual cells in the vestibular nuclei is not always clearly related to a single end organ (Baker et al, 1984), which suggests that there is some functional convergence of inputs from different end organs in some vestibular nuclear cells.

It should be noted that many, if not most, of the neurons in the vestibular nuclei do not receive direct inputs from the vestibular nerve. One prominent group of cells in the vestibular nuclei that does not receive direct inputs from the vestibular nerve is a group of cells that respond preferentially to stimulation of the contralateral vestibular nerve (Shimazu and Precht, 1966). In fact, the head movement sensitivity of most of the cells in the vestibular nuclei depends on bilateral activation of the vestibular end organs. Removal of one vestibular nerve typically reduces the head movement sensitivity of vestibular nuclear neurons approximately in half (Abend, 1978), which suggests that commissural pathways between the vestibular nuclei contribute significantly to the physiologic sensitivity of vestibular nuclear neurons.

Vestibular commissural pathways arise from every part of the vestibular nuclei except the dorsal lateral vestibular nucleus (Pompeiano et al, 1978). Although there is a tendency for a particular region of the vestibular nuclei to project heavily to its contralateral counterpart, there is also considerable divergence in the commissural pathways to other parts of the vestibular nuclei (Fig. 141-20). Functionally, the commissural pathways between the vestibular nuclei appear to play an essential role in the ability to compensate for unilateral vestibular lesions (Igarashi, 1984). Since most vestibular nuclear neurons fire spontaneously even when the head is not moving (Lisberger and Miles, 1980) and since most vestibular functions are organized bilaterally, an imbalance between the spontaneous firing rate of one vestibular nucleus compared to the other would most likely result in the central perception of head movement and dysfunctional operation of reflex pathways (for example, ocular nystagmus is usually produced when the vestibular nuclei are unilaterally damaged). The vestibular commissural pathways appear to play an important role in maintaining the balance in the output of the two sides.

Other inputs to vestibular nuclei

The vestibular nerve is not the only source of input to the vestibular nuclei. Many regions of the brain stem and the cerebellum also project to the vestibular nuclei. Most of the nonvestibular inputs arise from the flocculonodular lobe of the cerebellum (Langer et al, 1985b), from the fastigial nucleus (Carpenter and Cowie, 1985), and from regions of the brain stem in the vicinity of the vestibular nuclei, although the vestibular nuclei also receive inputs from the spinal cord and from nuclei located in the midbrain and caudal diencephalon. Although the function of each source of nonvestibular afferents to the vestibular nuclei is not completely known, the physiologic responses of vestibular nuclear neurons have been clearly shown to be affected by behaviors and stimuli not related to vestibular nerve activity. Perhaps the most common nonvestibular input to the vestibular nuclei is an input from the visual system. Most vestibular nuclear neurons that are sensitive to head movements are also sensitive to movements of the visual world; that is, they are sensitive to *optokinetic* stimuli (Waespe and Henn, 1979). The semicircular canals are relatively insensitive to low frequency (< 0.05 Hz) movements of the head. However, the visual system is capable of detecting extremely low frequency movements of the visual scene. Accordingly, the brain utilizes visual information to supplement the information obtained from the labyrinth. The anatomic pathways by which the visual optokinetic signals reach the vestibular nuclei have not been completely worked out, but several midbrain pretectal nuclei (in particular, the nucleus of the optic tract and the accessory optic nuclei) appear to play an essential role. These midbrain nuclei do not project directly to the vestibular nuclei themselves but rather project to other

brain stem nuclei, which in turn project to the vestibular nuclei (for example, the prepositus nucleus (Cazin et al, 1982) or to regions of the cerebellum that project to the vestibular nuclei (for example, visual signals reach the cerebellum via the inferior olive (Leonard et al, 1988) and the pontine nuclei (Kato et al, 1982)).

Pathways from the cerebellum to the vestibular nuclei not only contribute to the visual responsiveness of vestibular nuclear neurons, but also are essential for adaptive modification of the head movement sensitivity of vestibuloocular pathways and compensation for unilateral vestibular lesions. The cerebellar flocculus is particularly important for adaptive modification of VOR pathways (Ito, 1982; Lisberger and Miles, 1980; Miles and Lisberger, 1981). The Purkinje cells in this region of the cerebellar cortex are sensitive to optokinetic visual stimuli and to movements of small visual targets on the fovea (Lisberger and Fuchs, 1978; Stone and Lisberger, 1990; Waespe et al, 1983). When eye movements produced by vestibuloocular pathways fail to stabilize images on the retina, the Purkinje cells of the flocculus change their firing rate and modify the head movement sensitivity of some of the vestibular nuclear neurons that project to the extraocular motor nuclei.

As noted above, many of the neurons in the superior, medial, and ventral lateral vestibular nuclei change their firing rate during eye movements even when the head is not moving and the vestibular nerve activity is unchanging. Vestibular nuclear neurons that project to the extraocular motor nuclei fire during steady fixation, saccadic eye movements, and ocular smooth pursuit (Fuchs and Kimm, 1975; Tomlinson and Robinson, 1984). Apparently, the vestibular nuclei contribute to the generation of each of these oculomotor behaviors. The regions of the brain that provide these oculomotor-related inputs include the prepositus nucleus (McCrea and Baker, 1985), the interstitial nucleus of Cajal (Pompeiano and Walberg, 1957), and the pontine and medullary reticular formation (Strassman et al, 1986).

The spinal cord, particularly the cervical spinal cord, is another important source of nonvestibular afferents to the vestibular nuclei. The neurons in the dorsal lateral vestibular nucleus that project to the spinal cord also receive inputs from the spinal segments to which they project (Stampacchia et al, 1987). Neurons in the medial and ventral lateral vestibular nuclei that project to the extraocular motor nuclei receive inputs from the cervical spinal cord (Maeda, 1979). These inpurs are probably important for mediating the *cervical ocular reflex*, which is a reflex that can help the VOR to stabilize gaze during head movements, particularly when the labyrinth is damaged. These pathways provide a possible explanation for the nystagmus often seen after neck injury.

There are other nonvestibular inputs to the vestibular nuclei that are functionally important but whose anatomy is poorly defined. It is likely that some vestibular nuclear neurons receive inputs related to central autonomic functions and behavioral state (for example, alertness). The spontaneous firing rate and sensitivity to eye and head movements of many vestibular nuclear neurons are profoundly reduced during slow wave sleep or reduced alertness (unpublished observations) in spite of the fact that vestibular nerve activity is apparently unaffected. The central anatomic pathways that mediate these effects are unknown.

The major afferent connections to the vestibular nuclei are summarized in Fig. 141-21.

Efferent projection pathways from vestibular nuclei

The vestibular nuclei project to a large number of regions of the brain stem, cerebellum and spinal cord (see Fig. 141-22 for a summary diagram). In addition, the vestibular nuclei are highly interconnected. The instrinsic connections of the vestibular nuclei are not limited to the commissural pathways described above but also include connections between the various vestibular nuclei on the same side of the brain (Pompeiano et al, 1978). Some of the interconnections are made by collaterals of the major efferent pathways described below, but there is evidence that there are local circuit neurons in the vestibular nuclei that do not receive direct inputs from the vestibular nerve but inhibit the vestibular nuclear neurons that do (Shimazu and Precht, 1966). Fig. 141-22 provides an overview of the major vestibular efferent projections. All of the vestibular nuclei except the dorsal lateral vestibular nucleus contain neurons that project to the cerebellum. The cerebellar vermis, the flocculonodular lobe, and the fastigial nucleus are the regions of the cerebellum to which these vestibulocerebellar pathways project (Magras and Voogd, 1985). These are the revions of the cerebellum that are thought to be involved in coordinating movements of the axial musculature, the head, and the eyes. The output of the cerebellar cortex is organized in parasagittal efferent strips (Voogd, 1964). There is an efferent parasagittal cortical strip in the vermis that projects to the neurons in the dorsal lateral vestibular nucleus that gives rise to the lateral vestibulospinal tract. Another efferent strip in the vermis projects to the fastigial nucleus. Strips in the cerebellar cortex of the flocculonodular lobe project to the neurons in the superior, medial, and lateral vestibular nuclei that give rise to the vestibuloocular reflex pathways (Ito, 1982). Thus there are reciprocal connections between the vestibular nuclei and regions in the cerebellum that receive vestibular inputs.

The medial, superior, and ventral lateral vestibular nuclei give rise to major bilateral efferent projections to the regions of the brain stem that are involved in controlling eye movements. The vestibular nuclei give rise to an important set of reflex pathways involved in the VOR. The axons that make up these pathways usually join the medial longitudinal fasciculus (MLF) near the abducens nucleus, although one of the pathways related to the horizontal canal (the ascending tract of Deiters) and one of the pathways related to the posterior canal do not join the MLF until it is near the oculomotor nucleus (Gacek, 1971).

The function of the VOR is to stabilize vision during head movements. This is accomplished by moving the eyes at the same speed as the head but in the opposite direction. The VOR pathways are organized reciprocally such that the motor neurons that innervate each extraocular muscle receive both excitatory and inhibitory inputs from the vestibular nuclei. For example, the abducens nucleus (which innervates the lateral rectus muscle of the eye) receives excitatory inputs from vestibular neurons related to the contralateral horizontal semicircular canal and inhibitory inputs from neurons related to the ipsilateral horizontal canal (Baker et al, 1969). During head movements the firing rate of afferents that innervate the crista of the horizontal canal increases when the head turns in the ipsilateral direction and decreases when the head moves in the opposite direction. Since the vestibular nerve and the vestibular nuclei fire spontaneously (in the absence of any movement), neurons in the vestibular nuclei can increase or decrease their firing rate during head movements, depending on the direction of the movement. The VOR pathways, in turn, are organized in a reciprocal fashion such that when the excitatory vestibular pathways to extraocular motor neurons increase their firing rate, the inhibitory pathways decrease theirs. This bilateral "push-pull"

organization, in conjunction with vestibular commissural pathways, ensures that both labyrinthine end organs contribute to the generation of the VOR.

The direct pathways from the vestibular nuclei to the extraocular motor nuclei are not the only pathways that contribute to the generation of the VOR. There are also indirect pathways that help make the reflex eye movements more precise. The most important indirect pathways are mediated by neurons in the prepositus nucleus (McCrea and Baker, 1985) and in the interstitial nucleus of Cajal (King and Fuchs, 1977). These nuclei receive collateral inputs from vestibuloocular pathways and in turn project to the extraocular motor nuclei. These nuclei not only contribute to the generation of the VOR, but also play an important role in maintaining steady gaze. The prepositus nucleus is particularly important in maintaining eccentric horizontal gaze (Cannon and Robinson, 1987), and the interstitial nucleus of Cajal is important for maintaining eccentric vertical gaze (Anderson et al, 1984).

There is a second major efferent vestibular pathway thaty aids in gaze stabilization, the medial vestibulospinal tract. This pathways originates from cells in the medial and ventral lateral vestibular nuclei and projects bilaterally in the MLF to the ventral horn of the cervical spinal cord. Approximately half of these cells also contribute to the vestibulo-ocular reflex pathways via axon collaterals (Minor et al, 1990). The medial vestibulospinal tract functions to stabilize the head and the shoulders by generating neck muscle contractions that resist passive movements of the head (Wilson and Peterson, 1982).

The lateral vestibulospinal tract plays an important role in maintaining postural balance. This pathway arises from cells in the dorsal lateral vestibular nucleus and projects ipsilaterally to the ventral horn of the spinal cord, as far as the lumbar enlargement (Wilson and Melville-Jones, 1979). The cells in the dorsal lateral vestibular nucleus are particularly sensitive to tilting of the head (Pompeiano et al, 1988). The lateral vestibulospinal tract is tonically active and provides a powerful tonic excitatory synaptic input to postural extensor motor neurons. With unilateral labyrinthine lesions, the tonic excitatory input to ipsilateral postural extensors is reduced, particularly when visual cues are absent, and there is a tendency to fall toward the side of the lesion.

Vestibulothalamic pathways arise from cells in the ventral lateral vestibular nucleus and project to regions of the thalamic intralaminar nuclei that border the ventral posterior medial nucleus of the thalamus (nucleus centralis lateralis) (Lang et al, 1979). The vestibular nuclei also project to another thalamic nucleus, the ventral lateral geniculate nucleus. This nucleus is adjacent to the dorsal lateral geniculate nucleus and has anatomic connections that suggest it is involved in visual processing. Presumably, the vestibulothalamocortical pathways play a role in the conscious perception of vertigo, of self motion, in the absence of visual stimulation.

Summary

This chapter has provided an overview of the currents state of knowledge of the major anatomic features of the vestibular labyrinth and its central projections. Although a great deal is known about the vestibular system, a great deal remains to be discovered. For example, recent experiments in a number of laboratories have demonstrated that there is an otolith ocular reflex whose gain is a function of the target distance. This is an important new finding, but nothing is known about the anatomic pathways that underlie this reflex. Nonetheless, our knowledge is expanding rapidly and such information will no doubt be available soon.