Chapter 144: Physiology of the Vestibular System

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Overview of Vestibular Function

Vestibular reflexes

The basic elements of a vestibular reflex are the hair cell, an afferent bipolar neuron, an interneuron, and an effector neuron. Three neuronal reflexes already exist in the phylum Molusca, among which the class Cephalopoda has contributed to many classic anatomic and physiologic studies of gravitational reflexes (Budelmann, 1988). An important three-neuron reflex in the human being is the horizontal semicircular canal-ocular reflex. Clockwise angular acceleration in the plane of the horizontal semicircular canals results in an increased firing of the afferent nerve from the ampulla of the right horizontal semicircular canal. This afferent signal is carried to the vestibular nucleus situated in the dorsal lateral medulla. A neuron in the vestibular nucleus then transmits the signal to an effector neuron in the left abducens nucleus. Contraction of the left lateral rectus muscle initiates the compensatory deviation of the left eye to the left.

This simple example obviously does not provide the entire picture of the organization of the vestibuloocular reflexes because it does not take into account the bilateral symmetric canal system and the need for both excitation and inhibition of the different horizontal ocular muscles. With head rotation to the right, the increase in firing of the right horizontal ampullary nerve is accompanied by a decrease in the corresponding left nerve. In addition, some of the interneurons are inhibitory, and by means of these two classes of neurons, the afferent signal arriving from the ampullary nerve exerts a dual influence on the effector system: it excites the agonist group of muscles, and it inhibits the antagonist group.

The control of motor responses by the labyrinth is, therefore, a four-way mechanism (Fig. 144-1). Rotation to the right stimulates the ampullary nerve from the right horizontal semicircular canal, exerting an increased excitatory influence on the agonist (left lateral rectus) muscle and an inhibitory influence on the antagonist (right medial rectus) muscle. Because of the reciprocity between the two labyrinths, the ampullary nerve from the left horizontal semicircular canal diminishes its afferent output, thereby disfacilitating the excitatory influence in the antagonist muscle and disinhibiting the agonist muscle. The end result is contraction of the left lateral and right medical rectus muscles and relaxation of the left medial and right lateral rectus muscles. This push-pull pattern of organization applies to all labyrinthine-mediated reflexes.

Function of vestibular reflexes

At least three major functional roles for vestibular reflexes can be identified. The first is to maintain posture. Vestibular reflexes of this kind induce muscle contractions that produce negative geotropic movement or forces that compensate for steady changes in the direction of the force of gravity. If the pull of gravity on the body were unopposed by forces developed in the muscles, the body would collapse. Reflexes in this category depend on the function of the maculae but not on that of the semicircular canals. The second role is to produce "kinetic"

or transitory contractions of muscles for maintenance of equilibrium and ocular stability during movement. This category includes reflexes arising from both the semicircular canals during angular acceleration and the otolithic organs during linear acceleration. Most natural head movements contain both types of acceleration, and the vestibular reflexes act in combination to maintain equilibrium. A third role of vestibular reflex activity is to help maintain muscular tone, a role in which both maculae and cristae participate. The labyrinthine contribution to skeletal-muscular tone can be demonstrated by the change of posture that follows unilateral labyrinthectomy in normal animals. Tone is increased in the extensor muscles of the contralateral extremities and decreased in the ipsilateral extensor muscles. An even more striking demonstration of the vestibular role in the maintenance of muscular tone is the removal of decerebrate rigidity after sectioning of both vestibular nerves or destruction of the vestibular nuclei. The extensor rigidity that results from transection of the nervous system at the caudal end of the mesencephalon is markedly decreased when the tonic labyrinthine input is removed.

The high spontaneous firing rate of action potentials from the primary vestibular afferents provides a constant level of neural activity to the neurons in the vestibular nuclei. The peripheral vestibular influence also affects the response of the vestibular nuclei neurons to the converging inputs from other sensory systems and from neurons in the opposite side of the brain as well. By means of commissural and reverberating circuits, an integration, in the mathematical as well as the physiologic sense, takes place in the brain stem.

Vestibular interaction with other sensory systems

The maintenance of body equilibrium and posture in everyday life is a complex function involving multiple receptor organs and neural centers in addition to the labyrinth. Visual, somatosensory, and proprioceptive reflexes, in particular, must be integrated with vestibular reflexes to ensure postural stability. The prominent role of sensory interaction in orientation can already be appreciated in the behavior of gastropods. The invertebrate Hermissenda has only rudimentary vestibular and visual receptors, yet the two systems fully interact to control behavior (Goh and Alkon, 1984). Afferent signals from photoreceptors in the eye and from hair cells in the statocyst converge on interneurons in the cerebropleural ganglia, which control a putative motor neuron in each pedal ganglion. Excitation of the motor neuron produces turning of the animal's foot in the ipsilateral direction, consistent with the animal's turning behavior toward light. In humans, during most natural head movements, gaze stabilization is achieved by a combination of vestibular, neck proprioceptive, and visual inputs; the interaction can be synergistic or antagonistic. For example, when the vestibularly induced eye movements lie in a direction opposite to that required to maintain the desired gaze position, the visual reflexes override the vestibular reflex. The kind of head rotation that would produce compensatory eye movements in the dark (those suggested by the connections illustrated in Fig. 144-1) does not do so in the light if the subject fixates on a target moving in phase with the head. In this simple example, failure to override the vestibular signals could lead to disorientation.

Fig. 144-2 illustrates how different sensory systems provide information to a first line of individual central processors concerning orientation. These messages then converge to provide the common signals of eye movements and postural reflexes (in a common central processor). This common central processor is probably not localized to a specific neural

anatomic structure, although, as will be seen later, the vestibular nuclei are a major component of this processor. The functioning of the overall system is under adaptive control in a manner similar to that involved in other aspects of brain function and behavior (Houk, 1988). The adaptive processor uses information from cross-sensory modalities in executing automated tasks, such as the repetitive execution of an athletic skill or the adjustment in eye movements to the use of magnifying or minifying lenses (Melville Jones, 1985). Adaptive mechanisms are also important in selecting orienting strategies, such as maintaining equilibrium after a shift in one's center of gravity by moving knees, hips, arms, or all together (Nashner, 1985). The neuroanatomic correlate of the adaptive controller is only partially understood, although the cerebellum is clearly a major component of this system.

Clinical evaluation of vestibular function

Until recently, clinical vestibular tests were primarily system oriented; that is, they attempted to isolate the vestibular system from other systems. This approach had its limitations because oculomotor and postural control are complex functions that require coordinated interaction of multiple sensory and motor systems. During the last 2 decades, new methods have been developed to analyze objectively all the systems that control eye movements and posture. A large number of observations are being made that are producing an integrated and expanding picture of vestibular pathophysiology. This technology has created renewed interest in vestibular testing because of its importance for evaluation not only of inner ear disorders but also of various neurologic conditions.

This chapter systematically assesses the different components illustrated in Fig. 144-2. It begins with the peripheral vestibular apparatus, addressing the question of how the inner ear receptor organs transduce the forces associated with angular and linear head acceleration into biologic signals. Much of our understanding of how the end organ works has come from detailed measurements of the firing pattern of primary afferent neurons originating from the different vestibular receptors in many different animal species. This chapter reviews the spectrum of signals carried in primary afferent neurons and how these signals are modified after they arrive at the vestibular nuclei. The vestibular nuclei represent a major sensory integration center. Most neurons within the vestibular nuclei respond to multiple sensory signals (eg, visual, proprioceptive, somatosensory, and vestibular).

To interpret the results of clinical vestibular testing, one must have an understanding of the normal physiology of the vestibular reflexes. The vestibuloocular reflexes, in particular, will be extensively reviewed. The neurons in these reflexes connect the labyrinthine receptor organs with the 12 extraocular muscles of the eyes; thus it is possible through the measurement of eye movements, to correlate vestibular lesions with impairment of reflex functions. Although experimental investigations of vestibuloocular reflexes were initiated in the first quarter of this century, the contribution of each receptor organ and neural connection to the production of eye movements is still not completely known. The afferent signals from different vestibular receptors to each of the eye muscles overlap, and the central neural pathways lie so close to each other that often it is difficult to identify the receptor or pathway responsible for the deterioration of reflex function.

We will address the question of how the vestibular reflexes adapt to changes in the sensory environment or to lesions within their anatomic pathways. The importance of

adaptation within the vestibuloocular reflex is apparent when one considers that the amplitude of eye movement required of the vestibuloocular reflex changes by several percent whenever magnifying or minifying spectacles are used. An extreme example of such adaptation is the change in direction of the vestibuloocular reflex that occurs after one wears glasses with reversing prisms for several days (that is, the eyes will move in the same direction as that of the head instead of the opposite direction). The neuroanatomic and physiologic substrate for this capability is only partly understood, but the clinical importance of adaptive mechanisms is obvious. What are the strategies that patients use to compensate for loss of vestibular function? Why do some patients continue to complain of dizziness for months after such lesions, whereas other recover rapidly? Understanding the adaptive mechanisms is fundamental to understanding patient symptoms (which can be interpreted as a reflection of the failure to develop coping strategies) and for the design or rehabilitation programs.

Finally, we will assess the vestibular contribution to orientation. The vestibular nuclei project to higher cortical centers, and they receive reciprocal projections from these centers. Beginning at the vestibular nuclei, a stepwise integration of sensory signals occurs, reaching its maximum at the level of the cortex.

Peripheral Mechanisms

Labyrinthine fluids

The membranous labyrinth is enclosed within the bony channels of the otic capsule. A space containing perilymphatic fluid, a supportive network of connective tissue, and blood vessels lies between the periosteum of the bony labyrinth and the membranous labyrinth; the spaces within the membranous labyrinth contain endolymphatic fluid. The endolymphatic system develops in the embryo as an invagination of the germinal ectodermal layer (Anson, 1973). Starting as a simple fold, it soon becomes a closed cavity (the otocyst) isolated from the original ectoderm. By the end of the seventh week, the endolymphatic duct system is lodged in mesenchymal tissue, and by the fourteenth week, it attains the size that it will have in the adult ear. By successive infolding of the wall of the otocyst three main areas formed: the endolymphatic duct and sac, the utriculus and semicircular canals, and the sacculus and cochlear duct. The membranous cochlea holds the organ of Corti for the transduction of sound energy; and the utriculus, sacculus, and semicircular canals contain the receptors for sensing linear and angular motion. Together they constitute the membranous labyrinth proper. Finally, the endolymphatic duct provides a channel for the exchange of chemicals and to balance the pressure between the endolymphatic and subarachnoid spaces.

Dynamics of fluid formation

Perilymph is, in part, a filtration of cerebrospinal fluid (CSF) and, in part, a filtration from blood vessels in the ear (Salt and Konishi, 1986). The CSF communicates directly with the perilymphatic space through the cochlear aqueduct - a narrow channel 3 to 4 mm long with its inner ear opening at the base of the scala tympani (Fig. 144-3). In most instances, this channel is filled by a loose net of fibrous tissue continuous with the arachnoid. The size of the bony canal varies from individual to individual. Necropsy studies in some patients who died of subarachnoid hemorrhage or meningitis have revealed free passage of leukocytes and red blood cells into the inner ear, whereas in others, the cells were blocked from passing

through the aqueduct (Holden and Schuknecht, 1968). Blood cells have also been found passing into the internal auditory canal and through the porus canaliculi that contain the vestibular and cochlear nerves, suggesting another route for CSF perilymph communication. Probably the most important source of perilymph, however, is filtration from blood vessels from within the perilymphatic space, inasmuch as blocking the cochlear aqueduct does not appear to affect inner ear morphology or function (Kimura et al, 1974).

The most likely site for production of endolymph is the secretory cells in the stria vascularis of the cochlea and the dark cells in the vestibular labyrinth (Kimura, 1969; Salt and Konishi, 1986). Resorption of endolymph is generally agreed to take place in the endolymphatic sac. Die and pigment experimentally injected into the cochlea of animals accumulate in the endolymphatic sac; electron microscopic studies of the membrane that lines the sac reveal active pinocytotic activity (Lundquist, 1965).

Destruction of the epithelium lining the sac or occlusion of the duct results in an increase in endolymphatic volume in experimental animals (Kimura and Schuknecht, 1965). The first change is an expansion of cochlear and saccular membranes, which may completely fill the perilymphatic space. The anatomic changes resulting from this experiment are comparable to those found in the temporal bones of patients with Ménière's syndrome (either idiopathic or secondary to known inflammatory disease).

Fluid chemistry

The chemical compositions of the fluids filling the inner ear are similar to those of extracellular and intracellular fluids throughout the body. The endolymphatic system contains intracellular-like fluids with high potassium and low sodium concentrations, whereas the perilymphatic fluid resembles the extracellular fluid with low potassium, and high sodium concentrations (Salt and Konishi, 1986). The relationship between electrolytes and protein concentration in the different fluid compartments is shown in Fig. 144-3. The high protein content in the endolymphatic sac, compared with that in the rest of the endolymphatic space, is consistent with the sac's role in the resorption of endolymph. The difference in protein concentration between perilymph and CSF argues against a free communication between the compartments of these two fluids and in favor of an active process of perilymph production. The electrolyte composition of the endolymph is critical for normal functioning of the sensory organs bathed in fluid. Rupture of the membranous labyrinth in experimental animals causes destruction of the sensory and neural structures at the site of the endolymph-perilymph fistula (Schuknecht and El Seifi, 1963).

Hair cell

Phylogeny

The basic element of the labyrinthine receptor organs that transduces mechanical forces to nerve action potentials - the hair cell - is already developed in the statocysts of invertebrates (Budelman, 1988). Transducer cells are surrounded by supporting cells in specialized epithelial areas in the walls of the statocyst. In lower vertebrates a bundle of nonmobile cilia protrudes from the apical surface of the cylindric hair cells. The basal portion of the cell makes contact with many terminals of afferent and efferent nerve fibers. The

former carry information from the receptor to the central nervous system (CNS), and the latter provide feedback to the receptor cells from the CNS.

The increased complexity of the labyrinthine end organs, from an evolutionary point of view, is not limited to changes in gross anatomic features but is also expressed in the development of new structural details in the receptor cells (Lowenstein, 1974). Two types of hair cells occur in birds and mammals. Type I cells are globular or flask shaped with a single large chalicelike nerve terminal surrounding the base. The afferent fibers innervating these hair cells are among the largest in the nervous system (up to 20 microm in diameter). Type 2 cells are cylindric with multiple nerve terminals at their base (as in lower vertebrates).

The stereocilia are abound together at the top of the taller neighboring kinocilium, and when a force is experimentally directly applied to them, they move together with the rigidity of glass rods (Flock and Orman, 1983). Recent findings indicate that the physical properties of the stereocilia can influence the function not only of individual hair cells, but also of whole receptor organs. For example, the length and stiffness of the cilia in the organ of Corti influence the motion of the overlying basilar membrane (Flock et al, 1986). The stereocilia vary in length among hair cells of different organs and even within the same organ, depending on their location (Flock and Orman, 1983; Lewis, 1984). In the frog crista there are two cilium patterns: the stereocilia of cells at the center are tall and thick and the kinocilia are relatively short, whereas stereocilia of cells at the periphery are thinner and the kinocilia are very long. The former are stiffer and have, it is presumed, a higher resonance frequency than the latter. Hair cells of mammalian vestibular receptors also have at least two stereocilium patterns (Bagger-Sjöbach and Takumida, 1988).

Direction of force and hair cell activation

The adequate stimulus for hair cell activation is a force acting parallel to the top of the cell, resulting in bending of the hairs (Hudspeth, 1983). A force applied perpendicular to the cell surface (a compressional force) is ineffective in stimulating the hair cell. The stimulus is maximal when the force is directed along an axis that bisects the bundle of stereocilia and passes through the kinocilium. Deflection of the hairs toward the kinocilium depolarizes the hair cell, whereas bending in the opposite direction hyperpolarizes the cell (Flock et al, 1973). The effect is minimal when hair deflection is perpendicular to the axis of maximal excitation.

The anatomic basis for the hair cell's directional sensitivity is not known, but it is not dependent on the kinocilium. Hair cells in the mammalian cochlea do not have kinocilia yet they have the same direction sensitivity seen with other hair cells. Further, removal of the kinocilium from the hair cells of the bullfrog's sacculus does not alter the cell's directional sensitivity (Hudspeth, 1983). Electron micrographs of stereocilia do not show any obvious asymmetry in their cross section so that the directional response may be a property of the apical surface of the cell rather than the hair bundles themselves.

Physiology of hair cell activation

Since the hair cells are embedded in the epithelium of the membranous labyrinth, their apical surface is in contact with the endolymph in the interior of the organ (high in potassium) while the basal surface is in contact with the perilymph that surrounds the organ

(high in sodium). As with all living cells, the hair cell is selectively permeable, allowing some molecules to enter while others are kept out. This selective permeability is achieved through the opening and closing of channels that allow only certain types of ions to cross the cell membrane. The difference in potential between the inside of the cell and the surrounding fluid is called the membrane potential since it represents the drop in potential across the cell membrane. The hair-bearing surface of the cell membrane is morphologically different from the rest (thicker and more electron dense) - the so-called cuticular plate. During physiologic stimulation, ohmic resistance changes in proportion to the magnitude of hair deflection, which causes a modulated leakage of electric currents in a local circuit between the cuticular plate and other areas of the cell membrane (Fig. 144-4). The voltage drop produced in the vicinity of the hair cells by the current flow is known as the microphonic potential - the so-called generator potential - of these receptor organs (Dallos, 1985; Hudspeth, 1983). In contrast to nerve action potentials, the hair cell microphonic potentials have no refractory period (following the frequency of the stimulation above several thousand hertz), are highly resistant to anoxia, and may remain partially active after the animal's death. The electrical current associated with the generator potentials acts on the synaptic contacts between hair cells and nerve terminals by activating chemical transmitters to modulate the firing of action potentials by the afferent neurons.

Some hair cells may actively participate in the mechano-transduction process. Stereocilia of outer cochlear hair cells, which contain several contractile proteins, vary their length under direct electrical stimulation (Brownell, 1984). Therefore the physiologic properties of the stereocilia of cochlear hair cells may be influenced by electrical currents of neighboring physiologically activated cells. Likewise, their mechanical properties could be affected by postsynaptic potentials from efferent neurons innervating the receptor (Mountain, 1986). The stereocilia of the vestibular hair cells contain actin molecules and undergo an active change in stiffness if the concentration of calcium ions is experimentally changed (Orman and Flock, 1983). It is logical to expect that anatomic differences in stereocilia reflect important differences in the process of transducing head motion information into neural signals.

One of the most important findings concerning hair cell function was the discovery by Hoagland in 1932 that the afferent nerves from the lateral line organs of fish generated continuous spontaneous activity. This observation has subsequently been confirmed in all other sensory systems and represents a fundamental discovery in sensory physiology. Although the mechanism responsible for this spontaneous firing of action potentials is not known for certain, it may be that, even at rest, there is a steady stream of neurotransmitters diffusing across the hair cell-afferent nerve synapse. As indicated above, bending of the hairs toward the kinocilium results in an increase of the spontaneous firing rate, and bending of the hair away from the kinocilium results in a decrease. The spontaneous firing rate varies among different animal species and among different sensory receptors. It is thought to be greatest in the afferent neurons of the semicircular canals of mammals (up to 90 spikes/sec) and lowest in some of the acoustic nerve fibers innervating mammalian hair cells (1 to 2 spikes/sec) (Goldberg and Fernández, 1971a; Kiang et al, 1965).

Basis for stimulus specificity of vestibular receptor organs

The effective stimulus to the sensory cells is the relative displacement of the cilia

produced by application of mechanical force to their surroundings. The density of the otolithic membrane overlying the hair cells of the maculae is greater than that of the surrounding endolymph. The weight of this membrane produces a shearing force on the underlying hair cells that is proportional to the sine of the angle between the line of the gravitational vector and a line perpendicular to the plane of the macula (Fig. 144-5, A). The hair cell cilia in the cristae of the semicircular canals are embedded in the cupula, a jellylike substance of the same specific gravity as that of surrounding fluids. The cupula therefore does not exert a force on the underlying crista and is not subject to displacement by changes in the line of gravitational force. The forces associated with angular head acceleration, however, do result in a displacement of the cupula that stimulates the hair cells of the crista in the same way that displacement of the otolith stimulates the macular hair cells (Fig. 144-5, B). Because the mechanical properties of the "support and coupling" structures are different in these two organs, the frequency ranges at which the cilia can be moved by applied force are different.

Semicircular canals

Relationship between structure and function

The semicircular canals are three membranous tubes with a cross-sectional diameter of 0.4 mm, each forming about two thirds of a circle with a diameter of about 6.5 mm. They are aligned to form a coordinate system (Blanks et al, 1972, 1975). The plane of the horizontal semicircular canal makes a 30-degree angle with the horizontal plane; the other two canals are in vertical positions almost orthogonal to each other. The anterior canal is directed medically and laterally over the roof of the utriculus; and the posterior, behind the utriculus, is directed downward and laterally. The two vertical canals share a common opening on the posterior side of the utriculus. Since the planes of the canals are not aligned perfectly orthogonally, all angular movements stimulate at least two canals and often all three.

At the anterior opening of the horizontal and anterior canals and the inferior opening of the posterior canal, each tube enlarges to form the ampulla. A crestlike septum - the crista - crosses each ampulla in a perpendicular direction to the longitudinal axis of the canals (Fig. 144-5, B). The cupula extends from the surface of the crista to the ceiling of the ampulla, forming what appears to be a watertight seal (Ramprashad et al, 1984). In birds and lower mammals a higher proportion of type 1 hair cells are located in the ridge at the center of the crista, whereas type 2 hair cells predominate in the periphery (Correia et al, 1985; Fernández et al, 1988). In primates, type 1 hair cells predominate throughout the crista (Goldberg, 1990). In the three human cristae, there are about 23,000 hair cells (Rosenthall, 1972b) - representing a ratio of about 1.4 hair cells to afferent nerve fibers. Mammalian hair cells probably cannot regenerate after birth because function is permanently lost when they are damaged (Engstrom et al, 1966). In the cochlea of quail and chickens, however, supporting cells differentiate into sensory cells following destruction of hair cells after acoustic trauma (Corwin and Cotanche, 1988; Ryals and Rubel, 1988).

The hair cells within each crista are oriented so that all their kinocilia point in the same direction. In the vertical canals the kinocilia are directed toward the canal side of the ampulla, whereas in the horizontal canal they are directed toward the utricular side. The opposite morphologic polarization is the reason for the difference in directional sensitivity between the horizontal and vertical canals. The afferent nerve fibers of the horizontal canals

are stimulated by endolymph movement in the utricular or ampullopetal direction, and those of the vertical canals are stimulated by ampullofugal endolymph flow.

Dynamics: the pendulum model

The functional role of the semicircular canals was first linked to their gross and anatomic features by Flourens in 1842. While studying the auditory labyrinth in pigeons, he noted that opening a semicircular canal resulted in characteristic head movements in the plane of that canal. Several subsequent investigators proposed that movement of endolymphatic fluid within the canal was responsible for excitation of the cristae. It was not until the studies of Ewald in 1892, however, that a clear relationship was established between the planes of the semicircular canals, the direction of endolymphatic flow, and the direction of induced eye and head movements. Exposing the membranous labyrinth of the semicircular canals of pigeons, Ewald applied positive and negative pressures to each canal membrane to cause ampullopetal and ampullofugal endolymph flow. Three important observations that became known as Ewald's laws were (1) the eye and head movements always occurred in the plane of the canal being stimulated and in the direction of endolymph flow; (2) ampullopetal endolymph flow in the horizontal canal caused a greater response (that is, induced movements) than did ampullofugal endolymph flow; and (3) ampullofugal endolymph flow in the vertical canals caused a greater response than did ampullopetal endolymph flow.

Steinhausen (1927) and later Dohlman (1935) visualized the movement of the cupula during endolymph flow. By injecting India ink into the semicircular canals of fish, these investigators demonstrated that the cupula formed a seal with the ampullary wall and moved with the endolymph. Noting the similarity between the cupular movement and that of a pendulum in a viscous medium, Steinhausen proposed a model for the description of cupular kinematics, which became known as the pendulum model. Although the large movements observed by Steinhausen were later realized to be artifactual, the basic principle has been upheld by more recent experimental and theoretic studies. Further, physiologic verification of the model has been made by detailed study of the relationship between angular head acceleration and the flow of action potentials in isolated ampullary nerve fibers (see below).

Mechanism of stimulation

The pendulum model is the most useful didactic model for describing the physiologic properties of the semicircular canals and, as will be shown later, for describing the semicircular-induced reflexes, especially the vestibuloocular motor reflexes (Baloh and Honrubia, 1990). The cupula acts as the coupler between the force associated with angular acceleration of the head and the hair cell (the transducer of mechanical to biologic energy), leading to the production of action potentials in the vestibular afferent fibers. Because of the configuration and dimensions of the canals, the endolymph can move in only one direction along the cylindric canalicular cavity (see Fig. 144-5, B). According to Newton's third principle, when an angular acceleration (and hence a force, Møh(t)) is applied to the head, displacement of the cupula-endolymph system acting as a solid mass is opposed by three restraining forces: (1) an elastic force, Køc(t), caused by the cupula's springlike properties, (2) the force from the cupula-endolymph viscosity, Cø.c(t), and (3) an inertial force, Mø..c(t), caused by the fluid's mass. Cupular displacement can be described by the following equation, which is referred to as the equation of the pendulum model of semicircular canal function:

Mø..c + Cøc + Køc = Møh

where øc is the angular displacement of the cupula-endolymph system with respect to the wall of the canals; ø.c and ø..c are the first (velocity) and second (acceleration) time derivatives of the cupular displacement; ø..h is the angular acceleration of the head; M is the moment of inertia; C, the moment of viscous friction; and K, the moment of elasticity. Fig. 144-6 illustrates the relationship between the time course of head acceleration, head velocity, and cupula displacement as predicted by the pendulum model for three different types of angular rotation commonly used in clinical testing.

The moment-to-moment fluid displacement following *constant angular acceleration* has an exponential time course that can be determined by a more detailed mathematic treatment of the pendulum model (Van Egmond et al, 1949; Wilson and Melville Jones, 1979). The complete cupular trajectory as a function of time (t) after the application of the constant angular accelerations alpha is given by

Øc(t) = alpha (M/K) (1 - e-(k/c))

Accordingly, after a very long time, the exponential term vanishes (e-->0) and the cupular deviation becomes proportional to the magnitude of the acceleration alpha and to the coefficient M/K. Considering the exponential term e-(k/c), it can be appreciated that when t is equal to C/K, the value of the exponent is 1 and the exponential term has the value of e-1 = 0.37. The term within the parentheses on the right-hand side of equation 3 is now equal to 0.63. Measuring the time at which the response is 63% of the total provides an estimate of the value of C/K. This value is referred to in vestibular physiology as T1, the long time constant of the cupula. Another value, the so-called short time constant of the cupula or T2, defines the high-frequency sensitivity of the cupula. The product of M/k . K/C provides an estimate of T2 (Wilson and Melvill Jones, 1979).

According to the pendulum model, not only is the deviation of the cupula driven by a constant acceleration stimulus dependent on the restraining elastic force of the cupula, but also after the stimulus is terminated the same force becomes a restoring drive and the cupula returns to the resting position. If the cupula was deviated an amount of Øc, the return to the resting position takes place according to the following equation:

Øc(t) = Øce-tK/c

Thus the recovery process takes place with the same time constant T1 = C/K as that of the initial deviation. The deviation decays 63% for every interval of time (t) equal to T1, as shown graphically in Fig. 144-6, A.

The cupular displacement following a brief *impulse of angular acceleration* is given in 144-6, B. This type of angular acceleration, although the least natural, is of great value in clinical vestibular testing. An impulse of acceleration is generated by changing the velocity of the head (delta Ø.h) with the maximum acceleration possible. The maximum deviation of the cupula takes place almost immediately and is proportional to the magnitude of the instantaneous change in head velocity, Øc(t) = deltaØ.h. Of particular note, the cupular deviation thereafter decays exponentially with the same time course as that following the

constant acceleration stimulus. That is, it takes one time constant to return 63% of the maximum deviation.

Sinusoidal angular acceleration (see Fig. 144-6, C) most closely resembles natural head movements because movement in one direction is followed by movement in the opposite direction. Most natural head movements can be resolved into a series of sine waves with different frequencies and amplitudes. Two types of measurements are typically used to quantify the response to sinusoidal stimulation: a magnitude "gain" and a timing "phase" measurement. The gain is defined as the ratio of the output (cupula displacement) to the input (head acceleration or velocity) and the phase shift (in degrees), representing the timing between the output and the input. The relationship between the gain, phase, and frequency is commonly represented by a logarithmic plot called a Bode plot (Fig. 144-7). Some practical interpretations of the Bode plot for the equation of the pendulum model are as follows. For very low frequencies (less than 0.5 Hz) the gain increases linearly as frequency increases. For middle frequencies (0.1 to 10 Hz) the gain is constant; that is, cupular deviation is proportional to the velocity of the stimulus. Finally, for very high frequencies (greater than 10 Hz) gain decreases as a function of frequency. The phase relationship between the stimulus and response also varies with frequency (see Fig. 144-7, bottom). At low frequencies the response (cupular displacement) leads the stimulus (head velocity), reaching a maximum of 90 degrees or a quarter cycle at very low frequencies. In the middle frequency range the response and the stimulus are approximately in phase (as in Fig. 144-6, C). For very high frequencies the response lags behind the stimulus, reaching a maximum phase delay equivalent to another quarter cycle.

Innervation

Detailed study of the vestibular nerve in animals reveals a highly organized arrangement of the nerve fibers originating from the different inner ear receptors and from different parts of the same receptor. There is a continuous unimodal distribution of primary afferent neurons with regard to axon and cell body diameter (Fig. 144-8). The largest-diameter fibers innervate hair cells near the center of the crista, whereas the smallest-diameter fibers innervate hair cells in the periphery. Intermediate-size fibers are approximately equally distributed over the entire crista. Classic morphologists identified three types of nerve endings in the cristae. Large-diameter fibers had caliceal endings, small-diameter fibers had bouton endings, and intermediate-sized fibers had both types of endings (Lorente de Nó, 1933). With recently developed techniques for labeling individual neurons and fibers by intracellular injection of horseradish peroxidase, more detailed information has been obtained in the chinchilla regarding the fiber diameters associated with different nerve endings in different parts of the crista (Fig. 144-9) (Fernández et al, 1988). Neurons with large axon diameters innervate only a few hair cells with caliceal endings (type 1) in the center of the crista. Neurons with intermediate diameters have both bouton and caliceal endings and are more or less evenly distributed throughout the crista. Neurons with small axon diameters have only bouton endings and innervate multiple type 2 hair cells predominantly in the periphery. Of a sample of 368 fibers, 40 (11.1%) were caliceal units, 79 (21.5%) were bouton units, and 248 (67.4%) were dimorphic units (Fernández et al, 1988). Approximately the same distribution of fibers according to diameter is seen in the crista of the squirrel monkey and human (see Fig. 144-8).

Primary afferent neuron response

Detailed measurement of afferent nerve activity from the crista of several different animal species including primates revealed that the firing rate associated with physiologic rotatory stimulation follows qualitatively the prediction of the pendulum model (Baloh and Honrubia, 1990; Wilson and Melville Jones, 1979). That is, the magnitude of change in frequency of action potentials is roughly proportional to the theoretic deviation of the cupula. For example, during sinusoidal head rotation, at the frequencies of natural head movements, the firing rate follows the time course of cupular displacement shown in Fig. 144-6 (bottom trace). A sinusoidal change in firing frequency is superimposed on a rather high resting discharge (70 to 90 spikes/sec in the monkey). In this frequency range, the peak firing rate occurs at the time of the peak angular head velocity. For sinusoidal rotation of small magnitude, the modulation is almost symmetric about the baseline firing rate. For higher stimulus magnitudes, the responses become increasingly asymmetric. For the largest magnitudes, the excitatory responses can increase up to 400 spikes/sec, but the growth of inhibitory response is limited to disappearance of spontaneous activity. This asymmetry in afferent nerve response to stimuli of large magnitude at least in part explains Ewald's second and third laws, since his "pneumatic hammer" produced a massive stimulus to the semicircular canals (Ewald, 1892).

Just as there is a continuous spectrum of axon diameters, primary afferent neurons have a wide range of spontaneous firing rates and dynamic properties. It has proved useful to divide them based on the regularity of their spontaneous discharge rate (Goldberg et al, 1984, 1987). Neurons with the most irregular baseline firing rate (given by the coefficient of variation (CV) of the mean interspike interval) are the most sensitive to galvanic stimulation and have high-frequency dynamics that indicate a response to cupular velocity as well as to cupular displacement. Neurons with the most regular firing rate are the least sensitive to galvanic stimulation and have dynamics closer to those predicted by the pendulum model (see Fig. 144-7). As a general rule, a primary afferent's sensitivity to angular acceleration (in spikes per second per degree per second^2) is inversely related to the regularity of its baseline firing rate; that is, irregular units with high CV values have higher sensitivity than regular units with low CV value.

When the cristae are subjected to prolonged constant angular acceleration, a substantial proportion of nerve fibers undergo a slow decline in firing rate (adaptation) rather than maintaining a steady state as predicted by the pendulum model. Because of adaptation, the firing rate does not return to baseline after cessation of acceleration but, rather, drops to a lower level before returning to the resting level (Goldberg and Fernández, 1971b). Similar overshooting of the baseline occurs after stimulation with an impulse of acceleration. Instead of the monotonic response predicted by the pendulum model (see Fig. 144-6, B), the afferent nerve firing pattern exhibits a biphasic reaction with a prolonged secondary phase that slowly returns to baseline. This behavior is probably caused by hair cell transduction mechanisms. Adaptation is more pronounced in irregular neurons. As will be shown later, the vestibuloocular reflex also reflects this deviation from the predicted pattern (see Fig. 144-21, A and D).

Relationship between function and anatomy

Recently, it has been possible to study the anatomic and physiologic properties of a single primary afferent neuron by first recording the neuron's dynamic response to angular acceleration with a micropipette and then injecting it with horseradish peroxidase to study its anatomic connections. Initial studies in the bullfrog demonstrated that "irregular" neurons had thick, rapidly conducting fibers that preferentially innervated the central ridge of the crista, whereas "regular" neurons had thin, slowly conducting fibers that predominantly innervated the periphery (Honrubia et al, 1981). More recent studies in the chinchilla have correlated dynamic properties with patterns of nerve terminals in the crista (Baird et al, 1988). Of 56 semicircular canal units studied, 15 had caliceal endings, 1 had bouton endings, and 40 were dimorphic (both caliceal and bouton endings). All caliceal units were at the center of the crista and had "irregular" dynamic properties. The single bouton unit was in the periphery and had "regular" dynamic properties (bouton units were technically difficult to study because of their thin axons). Dimorphic units were both "irregular" and "regular" with the former usually innervating the center of the crista, and the latter the periphery. Surprisingly, the caliceal units at the center of the crista had a lower rotational sensitivity than dimorphic units with similar-size axons innervating the same region. Baird and associates (1988) postulated that because of their lower sensitivity, these caliceal units might extend the dynamic range of vestibular reflexes; that is, they would not become saturated by the large velocities of active head movements. Dimorphic units innervating different regions of the crista varied in their dynamic properties even though they contacted similar numbers of type 1 and type 2 hair cells. Apparently, the response dynamics of a canal afferent are determined by a transduction mechanism that varies as one proceeds from the ridge of the crista to the peripheral zones but not by the types or number of hair cells that it innervates.

Otolith organs

The membranous labyrinth forms two globular cavities within the vestibule: the utriculus and the sacculus. The sensory area of the sacculus - the macula - is a differentiated patch of membrane in the medial wall, hood shaped and predominantly in a vertical position. The oval-shaped utricular cavity connects with the membranous semicircular canals via five openings. The macula of the utriculus is located next to the anterior opening of the horizontal semicircular canal and lies mostly in a horizontal position in a recess on the anterior wall of the utriculus. It communicates by the utricular duct with the endolymphatic duct at the same level but by different openings from those of the saccular duct (see Fig. 144-3). Thus the endolymph in the superior or utricular part of the labyrinth is separated from that of the sacculus and cochlea by these tiny ducts. As noted earlier, blockage of these ducts leads to endolymphatic hydrops.

Each macula consists of a sensory membrane containing the receptor cells with a surface area less than 1 mm square that supports "a heavy load", the otolith (specific gravity approximately 2.7). The otolith is composed of calcareous material embedded in a gelatinous matrix and has a mean thickness of 50 microm (see Fig. 144-5, A). Even when the head is at rest, the calcareous material, because of its mass, exerts a force (F_g) on the receptor equal to the product of its mass and acceleration because of the gravitational pull of the earth (g), which at sea level is 9.8 m/sec^2 (see Fig. 144-5, A, right side). The distribution of Fg acting on the underlying sensory cells can be resolved into two vectors: one tangential (Ft) and the

other normal (Fn) to the surface of the receptor. The value of Ft is proportional to the sine of the angle of tilt (Ø). During linear head acceleration, the instantaneous force acting on the macula is the result of two vector forces: one in the direction opposite to that of the head acceleration and the other caused by gravitational pull. Again, the effective force producing otolith displacement is the resulting tangential force (Ft). In both cases the sensory cells of the maculae transmit information on the displacement of the otolith membrane to the CNS where reflexes are initiated to contract muscles that dynamically oppose the forces acting on the head and thus maintain equilibrium.

The calcareous material on the top of the otolith is called otoconia. The otoconia consists of small calcium carbonate crystals, ranging from 0.5 to 30 microm in diameter and having a density more than twice that of water. The striola is a distinctive curved zone running through the center of each macula. A higher proportion of type 1 hair cells are located near the striola than in the rest of the macula (Lindeman, 1969). The hair cells on each side of the striola are oriented so that their kinocilia point in opposite directions. In the utriculus the kinocilia face the striola, and in the sacculus they face away from it. As a consequence, displacement of the macula's otolithic membrane in one direction has an opposite physiologic influence on the set of hair cells on each side of the striola. Further, because of the curvature of the striola, hair cells are oriented at different angles, making the macula multidirectionally sensitive. Because the maculae are located off-center from the major axis of the head, they are subjected to tangential and centrifugal forces during angular head movements.

Mechanism of stimulation

As noted above during head movement, the calcified otolithic membrane is affected by the combined forces of applied linear acceleration and gravity and tends to move over the macula, which is mounted in the wall of the membranous labyrinth. The otolith is restrained in its motion by elastic, viscous, and inertial forces analogous to the forces associated with cupular movement. DeVries (1950) measured the displacement of the large saccular otoliths of several fish and obtained estimates of the forces restraining the otoliths to the maculae. He proposed a model, analogous to the pendulum model, that describes the dynamics of otolith displacement as that of a heavily damped, second-order lag system. Displacements caused by sinusoidal linear acceleration would be greatest at low frequency. At higher frequencies, the otolith displacement decreases by one half each time the frequency is doubled.

Innervation

As in the case of the crista, there is a unimodal distribution of nerve fiber diameters supplying each of the maculae. Large-diameter fibers are concentrated near the striola, whereas the thinner fibers innervate the periphery. Intermediate-size fibers are more or less equally distributed over the entire macula. In the chinchilla, the same three types of nerve terminals seen in the cristae are also seen in the maculae (Fernández et al, 1990). Caliceal units make up 2%, bouton units 12%, and dimorphic units 86% of the fiber population. Calyx units are limited to the striolar region, but even there dimorphic units outnumber caliceal units about 3 to 1 (Fernández et al, 1990). Dimorphic units in the striolar region contacted fewer hair cells on average than those in the peripheral extrastriola region (Fig. 144-10). For example, striolar dimorphic units contacted from 5 to 20 type 2 hair cells, whereas

extrastriolar dimorphic units contacted from 10 to 40 type 2 hair cells. Dimorphic units in the utricular macula on average had twice as many boutons as dimorphic units in the crista of the chinchilla.

Dynamics of primary afferent neurons

The nerve fibers innervating the maculae are activated by linear acceleration and by changes in the position of the head in space. Each neuron has a characteristic functional polarization vector that defines the axis of its greatest sensitivity. It is as though the terminal fibers of each afferent neuron are stimulated only by hair cells with kinocilia oriented in a given direction in space, forming one functional neuronal unit (such as those units shown in Fig. 144-10). The combined polarization vectors of neurons from both maculae cover all possible positions of the head in three-dimensional space. The majority of polarization vectors, however, are near the horizontal plane for the utricular maculae and the sagittal plane for the saccular macula (Fernández and Goldberg, 1976b). Diagrams of the functional polarization vectors determined by electrophysiologic analysis in the squirrel monkey are remarkably similar to morphologic maps that plot the polarization of hair cells within each macula. None of the neuronal units records a response to compressive forces; displacement of the hairs is the only adequate stimulus for the hair cell (Lowenstein and Roberts, 1949).

With the subject in the normal upright position, gravity does not stimulate most of the neuronal units of the utricular macula (because it is orthogonal to most polarization vectors). The average resting discharge of the macular units in this position is approximately 65 spikes/sec (Fernández and Goldberg, 1976a). The macula is roughly divided into a medial section and a lateral section by the striola. Because, in the utricular macula, hair cell polarization (the direction of the kinocilia) is toward the striola, ipsilateral tilt results in an increase in the baseline firing of the units medial to the striola and a decreased firing of the units lateral to the striola. Studies in the cat and monkey have found a 3:1 predominance of units that are excited by ipsilateral tilts as compared to those excited by contralateral tilts (Loe et al, 1973; Fernández and Goldberg, 1976a), whereas in the chinchilla the ratio is close to 1:1. This interspecies difference is at least in part caused by the fact that the relative area of the medial zone is large in the cat and monkey compared to the chinchilla (Goldberg et al, 1990a). Because of the curvature of the striola, many utricular macular units are also sensitive to forward and backward tilt. Since the saccular macula is in a sagittal plane when a subject is in the upright position most of its functional polarization vectors are parallel to gravity. Its neuronal units therefore are either excited or inhibited by 1 g of acceleration. The saccular macula exhibits less curvature than the utricular macula, and most of its units have a preferred dorsoventral orientation. Saccular units, at rest, discharge at a rate of essentially the same as that of utricular units (Fernández and Goldberg, 1976a).

As in the case of the cristae, the spontaneous firing rate subdivides two main classes of neuronal units in the maculae: regular and irregular (Fernández and Goldberg, 1976c). The irregular firing units adapt rapidly when stimulated with constant linear acceleration, are more sensitive to small changes in linear acceleration, and have a wider frequency response than the regular units. During stimulation with static tilts, the regular units maintain a constant ratio between the applied force and the response. During stimulation with sinusoidal linear acceleration (back-and-forth linear displacement), their sensitivity is constant up to 0.1 Hz but steadily declines at higher frequencies. These regular units therefore conform to many of the

predictions of the DeVries model (1950) of otolith function. In the chinchilla regular units outnumber irregular units by approximately a 3:1 ratio (Goldberg et al, 1990a). The irregular units respond not only to otolith displacement but also to the velocity of displacement. Following a change in head position, they undergo an immediate increase in firing followed by a decline. This difference between the presumed displacement of the otolith membrane and the afferent unit response may be related to mechanical linkage between the hair cell cilia and the membrane (Lim, 1973).

As in the chinchilla crista, irregular units in the macula are more numerous in the striolar region, whereas regular units predominate in the periphery. Also as in the crista, caliceal units are always irregular and bouton units regular; dimorphic units can be either. Dimorphic units near the striola are typically irregular, whereas those in the periphery are regular. Regular dimorphic units tend to innervate large numbers of type 2 hair cells compared to irregular dimorphic units, but this is only a qualitative difference, and some units with identical numbers of hair cells have markedly different dynamic characteristics. Goldberg et al (1990b) concluded that the response dynamics of both the canal and utricular afferents are primarily determined by transduction mechanisms that vary as one proceeds from central to peripheral zones and are not related to the discharge regularity or to the types and number of hair cells innervated.

Central Processing

Vestibular nuclei

Vestibular signals originating in the two labyrinths first interact with signals from other sensory systems in the vestibular nuclei. Only a fraction of the neurons in the vestibular nuclei receive direct vestibular connections, and, with perhaps the exception of the interstitial nucleus of the vestibular nerve, most neurons receive afferents from other sources, including the cervical area, the cerebellum, the reticular formation, the spinal cord, and the contralateral vestibular nuclei (Precht, 1979). Consequently, efferent signals from the vestibular nuclei reflect the interaction of these various systems.

Classification of secondary vestibular neurons

Following stimulation of the vestibular nerve with a single brief electric pulse, two different groups of secondary vestibular neurons have been identified based on their relationship to the field potential produced in the vestibular nuclei (Fig. 144-11) (Precht and Shimazu, 1965; Shimazu, 1983). This field potential consists of three components: an initial positive-negative deflection from action currents in the primary vestibular fibers; a negative deflection (N1) with a short latency less than 1 msec, generated by monosynaptically activated secondary vestibular neurons and fibers; and a delayed negative deflection (N2) with a latency of about 2.5 msec, generated by multisynaptically activated neurons and fibers (see Fig. 144-11, A). By carefully placing microelectrodes in the vicinity of or inside secondary vestibular neurons and tailoring the electrical stimuli, it has been demonstrated that some neurons produce action potentials at the same time as the intracellular N1 wave with latencies between 0.5 and 1.0 msec (see Fig. 144-11, B), suggesting that they receive monosynaptic input. Other neurons produced delayed action potentials (see Fig. 144-11, C), suggesting that they are activated through multisynaptic connections. Only about 75% of neurons in the vestibular

nuclei are activated by nerve stimulation, and approximately half of these are monosynaptically activated (Shimazu, 1983). All monosynaptic connections are ipsilateral and excitatory. Among the monosynaptically activated neurons, about 37% respond to small electrical stimuli with very short latencies that activate only the thickest, most sensitive irregular primary afferents (Goldberg et al, 1987). The rest of the neurons respond to larger electrical currents, suggesting that they receive a predominant input from thinner, regular afferents. However, it would be wrong to view secondary vestibular neurons as narrowly tuned channels, each receiving only a single kind of primary afferent input. Most vestibular nuclei neurons, even those predominantly related to regular or irregular afferents, receive a broad range of afferent inputs.

The most simple physiologic classification of secondary vestibular neurons consists of two major groups (Shimazu, 1983): type 1 neurons are excited and type 2 neurons are inhibited by ipsilateral rotation of the head (Fig. 144-12). The former are monosynaptically activated by ipsilateral primary afferents, whereas the latter receive their input via commissural connections either from neurons in the reticular substance or directly from contralateral type 1 neurons (as shown in Fig. 144-12). Type 1 neurons can be excitatory or inhibitory, whereas type 2 neurons are always inhibitory. Contralateral labyrinthine stimulation excites type 2 neurons, and they in turn inhibit ipsilateral type 1 neurons. It follows that during head rotation the activity of ipsilateral type 1 neurons is enhanced by excitation from the ipsilateral labyrinth and by decreased inhibition from neighboring type 2 neurons (whose input from the contralateral type 1 neurons has simultaneously decreased).

Organization of vestibuloocular reflexes

Much of our knowledge about the physiology of secondary vestibular neurons has come from studies of neurons that participate in the vestibuloocular reflexes. The basic organization of the vestibuloocular reflexes is shown in Fig. 144-13. Type 1 secondary neurons make direct contact with oculomotor neurons and provide axon collaterals to chains of interneurons located on the same side of the brain stem and cerebellum (Lorente de Nó, 1933). These interneurons along with the commissural connections from the contralateral side provide positive feedback to the secondary vestibular neurons (Shimazu, 1983). Although the response of the contralateral neurons during physiologic stimulation is opposite in sign to that of the ipsilateral neurons, the inhibitory interneurons convert the commissural pathway to a positive feedback loop. The net effect is to provide a temporal integration of signals from different vestibular receptors by sustaining the activity in the vestibular nuclei beyond that of the primary afferent signal, so-called velocity storage (Raphan et al, 1979). The effect of velocity storage is graphically illustrated in Fig. 144-13, B. After an impulse of head acceleration, the time constant of the oculomotor response (Tvor) is prolonged beyond that of the primary afferent response (T1) because of feedback onto the secondary vestibular neurons. The interneurons in these feedback pathways can be viewed as valves controlling the spontaneous activity and dynamic properties of the secondary vestibular neurons.

Many of the direct connections from the vestibular nuclei to the oculomotor neurons are part of a large fiber bundle, the medial longitudinal fasciculus (MLF), lying along the floor of the fourth ventricle. This fiber bundle extends from the cervical cord to the reticular substance of the midbrain and thalamus, providing an interconnecting pathway between the vestibular and oculomotor complex in the rostral brain stem as well as connections to the

abducens nuclei in the middle brain stem (Evinger et al, 1977). In addition to sending axons into the third and fourth nuclei, the MLF sends collaterals into the reticular substance of the midbrain and thalamus.

Vestibuloocular pathways

Semicircular canal: oculomotor connections

Each semicircular canal is connected to the eye muscles in such a way that stimulation of a canal nerve results in eye movement approximately in the plane of that canal. For example, stimulation of the left posterior canal nerve excites the ipsilateral superior oblique and the contralateral inferior rectus muscles while inhibiting the ipsilateral inferior oblique and contralateral superior rectus. An oblique downward movement in the plane of the left posterior canal is the end result. By systematically recording in different vestibular and oculomotor nuclei after stimulation of each semicircular canal, it has been possible to trace the main disynaptic excitatory and inhibitory pathways connecting the semicircular canals with the extraocular muscles (Fig. 144-14) (Uchino and Suzuki, 1983; Uchino et al, 1983). As a general rule, excitatory connections run in the contralateral MLF and inhibitory connections in the ipsilateral MLF (Ohgaki et al, 1988). The connections illustrated in Fig. 144-14 are only part of the picture, however, Inasmuch as the planes of the semicircular canals are not exactly aligned with the planes of the three pairs of eye muscles, a spatial transformation from the canal to muscle coordinates must occur if eye movements are to compensate for head movements. In other words, it is not adequate to simply connect afferents from a single canal to a set of eye muscles (as shown in Fig. 144-14); other connections must also exist. Preliminary studies of labeled secondary vestibular neurons identified as part of the canal ocular reflex indicate that the spatial transformations occur through both a convergence of signals at the level of the vestibular nuclei and a divergence of signals at the level of the oculomotor nuclei (McCrea et al, 1987a, 1987b; Permutter et al, 1988).

Otolith-oculomotor connections

The pathways from the maculae to the extraocular muscles are less clearly defined than are those from the semicircular canals. The latency of eye muscle activation after stimulation of the utricular and saccular nerves is similar to that recorded after semicircular canal nerve stimulation; disynaptic pathways also exist from the maculae to the extraocular muscles (Blanks et al, 1978; Eckmiller, 1982; Schwindt et al, 1973). Because of the varied orientation of hair cells within the maculae, simultaneous stimulation of all the nerve fibers coming from a macula produces a nonphysiologic excitation, and the induced eye movements fail to mimic the naturally occurring ones. Selective stimulation of different parts of the utriculus and sacculus results in mostly vertical and vertical rotatory eye movements (Fluur and Mellström, 1971; Suzuki et al, 1969). As one would expect, stimulation on each side of the striola produces oppositely directed rotatory and vertical components. Each of the vertical eye muscles appears to be connected to specific areas of the maculae so that groups of hair cells whose kinocilia are oriented in opposite directions excite agonist and antagonist muscles.

Relationship between canal afferent signals and eye movements

The semicircular canal ocular reflexes produce eye movements that compensate for head rotations. The various transformations involved in this process are illustrated in Fig. 144-15. The natural stimulus for the semicircular canals is head angular acceleration (Fig. 144-15, b). However, during sinusoidal rotation at the frequencies of natural head movements, because of the viscoelastic properties of the canal-cupula complex (as described by the pendulum model) the vestibular nerve firing rate (Fig. 144-15, e) is in phase with head velocity rather than head acceleration. Thus the equivalent of one step of mathematic integration (in other words a 90-degree phase shift) has occurred. The normal reflex response produces a compensatory eye movement equal and opposite to that of the head movement (compare a and g in Fig. 144-15). This eye movement results from activation of, among others, the abducens nerve to the left lateral rectus muscle (Fig. 144-15, f) during ampullopetal stimulation of the right cupula-vestibular nerve (Fig. 144-15, d and e). However, the recorded activity in the abducens nerve lags behind the activity in the vestibular nerve by an additional 90-degree delay. This raises a key question first addressed by Skavenski and Robinson (1973): What produces the phase shift between the firing rates of the vestibular and abducens nerves (between e and f in Fig. 144-15)? To answer the question, they introduced the concept of an oculomotor integrator, a hypothetical neural network that integrates, in a mathematic sense, velocity-coded signals (such as those originating in the vestibular end organ) to position coded signals required by the oculomotor neurons. Although the concept of neural integration is now generally accepted, the specifices are still debated. Some feel it is "localized" in a region of the brain stem (Cannon and Robinson, 1985; Cheron and Godeaux, 1987) or cerebellum (Carpenter, 1972), but others consider it "a distributed property" of the feedback pathways shown in Fig. 144-13 (Goldberg et al, 1987). Galiana and Outerbridge (1984) developed a mathematic model to show how these feedback pathways, particularly those via the commissural connections, could produce the necessary integration.

Although the vestibuloocular reflex (VOR) operates as an integrating angular accelerometer for frequencies greater than 0.1 Hz, at lower frequencies there is a progressive phase lead of eye velocity relative to head velocity reaching a maximum of 90 degrees at about 0.001 Hz. Velocity storage within the central VOR feedback pathways improves the low-frequency phase deficit of incoming primary afferent signals but does not correct it completely. As will be shown later, this low-frequency phase shift of the VOR is of little functional significance, inasmuch as natural head movements stimulate visual and vestibular reflexes and the combined responses are perfectly compensatory at low frequencies. It does have important implications for clinical testing, however, because an increase in the low-frequency phase lead is a nonspecific sign of damage to the canal ocular reflex (for example, see Fig. 144-26).

Neural mechanisms for production of nystagmus

Secondary vestibular neurons

Type 1 secondary vestibular neurons (excitatory and inhibitory) identified as part of the horizontal vestibuloocular reflex show a characteristic pattern of discharge during induced nystagmus (Fig. 144-16). During the slow phase the secondary vestibular neurons fire tonically a slight increase in rate just before the onset of a fast component. With the onset of

a fast component they pause. Whether all secondary vestibular neurons pause for fast components is debated, but Berthoz et al (1989) reported that all secondary neurons identified as part of the horizontal vestibuloocular reflex in the alert cat paused during fast components. The firing rate of secondary neurons during the slow phase of nystagmus has both a head velocity and an eye position component. In other words, secondary vestibular neurons that are part of the horizontal canal ocular reflex carry a signal that is intermediate between that of the primary vestibular afferents (see e in Fig. 144-15) and that of the abducens nerve (see f in Fig. 144-15). Some investigators have identified two types of secondary vestibular neurons based on whether the neuron contained only a head velocity signal or a combined head velocity-eye position signal (the former being called vestibular pause (VP) cells and the latter tonic vestibular pause (TVP) cells). However, Berthoz et al (1989) argued that, at least in the cat, if the animal is properly alerted, all secondary vestibular neurons identified as part of the horizontal canal ocular reflex exhibit a component of eye position sensitivity. Drowsiness effectively abolishes the eye position signal. When the animal is maximally alert, eye position sensitivity of secondary vestibular neurons is roughly proportional to head velocity sensitivity. Presumably, secondary vestibular neurons receive the eye position signal from the neural integration discussed earlier.

Burst cells

Groups of neurons located in the reticular formation in the paramedian pons and mesencephalon are specialized to fire before the onset of rapid eye movements (saccades or nystagmus quick phases). These neurons fire with a high-frequency burst proportional to eye velocity during the rapid eye movement. Two main types of burst neurons have been identified: excitatory burst neurons (EBNs) and inhibitory burst neurons (IBNs) (Fig. 144-17) (Shimazu, 1983). EBNs provide the burst of excitatory activity to the abducens nucleus during an agonist fast component and the pause in type 1 secondary vestibular neurons during an ipsilateral fast component. This pause is achieved through direct connections from EBNs to ipsilateral type 2 secondary vestibular neurons, which in turn inhibit type 1 neurons (Fig. 144-17). The EBNs also account for the weak bursting activity of type 1 secondary vestibular neurons during contralateral fast components. The abrupt inhibition of ipsilateral type 1 secondary vestibular neurons results in a sudden disinhibition of contralateral type 1 neurons via the type 2 neurons (Berthoz et al, 1989). IBNs account for the pause in contralateral abducens motor neurons during an ipsilateral fast component (Fig. 144-17).

Pause neurons

Another group of neurons in the reticular formation near the midline, at the level of the abducens, interrupt their background activity before rapid eye movements in all directions. These neurons fire at a remarkably regular baseline rate (about 200 spikes/sec in the monkey) and then abruptly pause just before the onset of rapid eye movements; they resume their regular firing at the end of the rapid eye movement. These neurons produce monosynaptic inhibitory potentials (IPSPs) in both IBNs and EBNs (Curthoys et al, 1984; Furuya and Markham, 1982). They therefore trigger the onset of nystagmus quick phases.

Oculomotor neurons

The relationship between the firing rate of oculomotor neurons and the movements of

the eyes during each phase of nystagmus has been studied most extensively. During the production of agonist slow components (see Fig. 144-16, A) the membrane potential is slowly depolarized by excitatory postsynaptic potentials (EPSPs) arriving via the vestibuloocular pathways discussed in the previous sections. Toward the end of the slow component, the membrane potential rapidly becomes hyperpolarized, and the motor neuron abruptly terminates its discharge. This hyperpolarization is produced by the IBNs (Hikosaka et al, 1978). The opposite membrane potential changes and abducens nerve firing rate occur when the neuron is participating antagonistically in the production of the slow component of nystagmus (see Fig. 144-16, B). In this case, the sudden depolarization recorded intracellularly and the burst of activity in the abducens nerve originate from the EBNs.

Measurement of the relationship between motor neuron firing rates and eye movements induced by vestibular or visual stimuli has shown that the motor neurons behave the same, regardless of the nature of the stimulus (Robinson, 1970). Almost all oculomotor neurons exhibit a threshold above which they increase their firing rate roughly in proportion to the change in eye position in the orbit. A small percentage of the change in firing rate (approximately 20%) is proportional to the velocity of the eye movement. It is as though the firing rate of oculomotor neurons were designed to overcome the elastic and viscous forces (roughly in a ratio of 5:1) restraining the eye in the orbit. This relationship can best be appreciated by examining the rate of firing of an oculomotor neuron associated with a visually induced refixation saccade, in which the goals are to move the eyes as rapidly as possible from one position in the orbit to another and to maintain the new position once it is reached. During the high-velocity saccade, the oculomotor neuron increases its firing rate to a high level to compensate for the viscous drag of the eye ligaments (reaching firing rates as high as 800 to 1000 spikes/sec). Once the new position is reached, a much lower rate of discharge produces compensation for the elastic restraining force and maintains the new position. Although the reflex pathways for vestibular and visually induced eye movements involve different neuronal circuits, the motor neurons governing the extrinsic eye muscles fire in the same manner regardless of the original sensory input.

Neural mechanisms of cervical-vestibular interaction

Ocular stability during most natural head movements results from a coordinated interaction of signals originating in the vestibular, visual, and neck receptors. The compensatory nature of neck-induced eye movements has been documented in many different animals. DeKlyn (1922) showed that if one holds an animal's head stationary and displaces the body, a compensatory eye deviation occurs, which tends to preserve the relationship between gaze and the body axis. Nonfoveate animals, such as the rabbit, exhibit clear compensatory eye deviations because they possess almost no spontaneous eye movements (Gresty, 1976). Cervicoocular and vestibuloocular reflex interaction is more difficult to study in humans because of the dominance of voluntary and visually controlled eye movements. Very few investigators have quantitatively assessed eye, head, and neck movement coordination in humans, and the clinical significance of lesions involving the cervicoocular reflex pathways is uncertain.

Animal studies have shown that the cervicoocular reflex originates from nerve endings in the ligaments and capsules of the upper cervical articulations (Hikosaka and Maeda, 1973; McCouch et al, 1951). The reflex can be induced by electrically stimulating the capsules of

the upper cervical joints, the C1 to C3 dorsal roots, and the high cervical spinal cord. Reflexes are not induced by stimulating the superficial muscles or skin of the neck. Bilateral sectioning of the high cervical dorsal roots or the application of local anesthetic around the cervical articulations abolishes the cervicoocular reflexes. Unilateral interruption of the neck ocular reflex pathways produces nystagmus in rabbits, cats, and monkeys when fixation is inhibited, although no consistent relationship exists between the side of dorsal root involvement and the direction of nystagmus (DeJong et al, 1977; Igarashi et al, 1972). As with vestibuloocular reflexes, the eye muscles are either excited or inhibited by neck stimulation, depending on whether the muscle is agonistic or antagonistic for the required compensatory movement.

Electrophysiologic experiments suggest that cervicoocular reflexes are mediated via the vestibular nuclei (primarily the medial and descending nuclei) (Hikosaka and Maeda, 1973; Rubin et al, 1975). The precise projections of the neck afferents to each vestibular nucleus are only partially known, but it can be anticipated that inasmuch as the neck-induced eye movements compensate for displacement in the precise plane of body motion, the vestibular nuclei must contain a discrete topographic representation of cervical afferents in a manner similar to that of the vestibular afferents. Electrical stimulation of the high cervical dorsal roots in the cat produces evoked potentials in the contralateral vestibular nuclei (Hikosaka and Maeda, 1973) followed by excitation of the abducens nucleus ipsilateral to the neck stimulation and inhibition of the contralateral abducens nucleus. In addition, stimulation of the cervical dorsal roots enhances the amplitude of action potentials in the ipsilateral abducens nerve induced by contralateral vestibular nerve stimulation and inhibits action potentials in the contralateral abducens nerve induced by ipsilateral vestibular nerve stimulation. Vestibuloocular and cervicoocular reflex interaction therefore results from a convergence of neck and semicircular canal afferents on secondary vestibular neurons.

Neural mechanisms of visual-vestibular interaction

Shortly after it was demonstrated by Dichgans and co-workers (1973) that neurons in the vestibular nuclei of goldfish responded to visual stimuli, similar observations were made by other investigators in a variety of animals under a variety of experimental conditions. Waespe and Henn (1987) found that every neuron in the vestibular nucleus of alert monkeys that responded to horizontal rotation of the animal in the dark also responded to horizontal rotation of the visual surround. During combined visual-vestibular stimulation, neurons were maximally excited (or inhibited) when the vestibular nystagmus and the optokinetic nystagmus were in the same direction (that is, the background moved in the opposite direction of the monkey). If the optokinetic drum was mechanically coupled to the turntable so that both rotated together, nystagmus was reduced and neuronal activity was attenuated, compared with pure vestibular stimulation in the dark (Fig. 144-18). The vestibular nuclei represent a major visual-vestibular interaction center.

Afoveate animals

In afoveate animals the subcortical, accessory optic system is the predominate pathway for visual-vestibular interaction (Collewijn, 1975; Precht and Strata, 1980; Simpson, 1984). This system includes a group of nuclei at the mesodiencephalic border, which, like the lateral geniculate nucleus, receives direct retinal projections but, unlike the lateral geniculate, projects

directly to the brain stem and cerebellum. The most prominent cell group of the accessory optic system, the nucleus of the basal optic root, is identifiable in all classes of vertebrates. Lázár (1973) found that optokinetic responses are abolished in frogs after destruction of the basal optic root nuclei, whereas ablation of the lateral geniculate nuclei and superior colliculi did not affect optokinetic responses.

Electrophysiologic studies in rabbits have demonstrated projections from the retina to the flocculonodular lobe of the cerebellum via the accessory optic system (Maekawa and Takeda, 1975, 1976). Microelectrode recordings in the accessory optic nucleus of the rabbit and the cat reveal units that show a strong response to slow, full-field retinal stimulation (Collewijn, 1975; Hoffman and Schoppman, 1975). Temporonasal movements of large patterns (rich in texture) evoke the strongest response. Neuroanatomic studies using horseradish peroxidase to map the connections between the accessory optic system and the flocculus reveal two separate pathways: one direct and the other indirect synapsing in the inferior olive (Branth and Karten, 1977; Winfield et al, 1978).

The principal anatomic pathways for visual vestibular interaction in the rabbit as proposed by Ito (1975) are shown in Fig. 144-19. Retinal sensory information reaches the inferior olives by way of the accessory optic tract and the central tegmental tract. Neurons in the inferior olives activate Purkinje cells in the flocculus, nodulus, and adjacent parts of the cerebellum. These areas of the cerebellum also receive primary vestibular afferent fibers and secondary vestibular fibers originating mostly in the medial and descending vestibular nuclei. Outflow from the cerebellar (Purkinje cells terminates at secondary vestibular neurons and runs in the adjacent reticular substance. Although Purkinje's cell outflow to the vestibular nuclei is inhibitory (as with all Purkinje's cell output), because it ends on both excitatory and inhibitory vestibular neurons, it can enhance or inhibit the vestibuloocular reflex. Several types of experimental data confirm the floccular role in mediating visual-vestibular interaction in the rabbit. Electrical stimulation of the flocculus inhibits nystagmus by physiologic and electrical stimulation of the vestibular nerve (Ito et al, 1974). The reflex contraction produced in agonist extraocular muscles by electrical stimulation of an isolated canal nerve is inhibited by prior stimulation of the flocculus, the accessory optic tract, or the optic chiasm (Maekawa and Simpson, 1972). Finally, in animals with lesions of the flocculus or inferior olives, the vestibuloocular reflex cannot be modulated by visual stimulation (Ito et al, 1974).

Foveate animals

With the development of the fovea, cortical pathways become progressively more important in visual-vestibular interaction. Recent anatomic and physiologic studies in primates indicate that the visual signals reach the brain stem for interaction with vestibular signals by a complex cascade of interconnecting pathways. In contrast to the rabbit and cat, neurons in the pretectal complex of the monkey receive predominate input from the visual cortex and respond equally well to small spots or large random dot patterns moving through their receptive field (Hoffman et al, 1988). Further, they respond similarly to monocular or binocular stimulation; that is, they do not exhibit the temporonasal preponderance seen in afoveate animals. Electrical stimulation of the nucleus of the optic tract in alert monkeys evokes horizontal nystagmus with a slow buildup in slow-phase velocity followed by afternystagmus in the same direction (Schiff et al, 1988). The rising time course in slow-phase velocity is similar to the slow buildup in optokinetic nystagmus (OKN), and the falling time

course of the afternystagmus parallels that of optokinetic afternystagmus. The striate cortex (Dow, 1974), the superior temporal sulcus (particularly middle temporal (MT) and medial superior temporal (MST) areas) (Albright, 1984; Maunsell and Van Essen, 1983; Tanaka et al, 1986; Zeki, 1980), and the posterior parietal cortex (Robinson et al, 1978; Sakata et al, 1983) are the key cortical areas in the monkey for processing retinal motion information. These cortical centers project heavily to the dorsal-lateral pontine nucleus (DLPN), which is a primary source of afferents to the flocculus and vermian areas 6 and 7, two cerebellar areas involved in the regulation of eye movements (May and Anderson, 1986; May et al, 1988). Neurons in the DLPN exhibit a directionally selective response to movement of discrete spots and large backgrounds, and microstimulation in the region of DLPN causes a short latency modification of the velocity of an ongoing-pursuit eye movement (May et al, 1988).

In the monkey, lesions of the parietotemporal region (Lynch and McLaren, 1982), the DLPN (May et al, 1988), and the flocculus (Zee et al, 1981) result in an impairment of (1) smooth pursuit, (2) the initial rapid raise in OKN slow-phase velocity, and (3) visual vestibular interaction requiring the foveal pursuit pathway (for example, fixation suppression of vestibular nystagmus with a foveal target). By contrast, lesions of the pretectal nuclei (nucleus of the optic tract) impair OKN but not pursuit (Kato et al, 1986).

Organization of vestibulospinal reflexes

It is helpful to consider the similarities and differences between the ocular and spinal vestibular reflexes as an introduction to the organization of vestibulospinal reflexes. The effector organ of the vestibuloocular reflexes are the extraocular muscles, and those of the vestibulospinal reflexes are the antigravity muscles - the extensors of the neck, trunk, and extremities. The same push-pull mechanism exists for controlling the balance between the extensor and flexor skeletal muscles as for the eye muscles (see Fig. 144-1). A major difference between the organization of ocular and spinal reflexes is the increased complexity of spinal muscle response, compared with the eye movements produced by an agonist and antagonist muscle. Even a simple movement about an extremity joint in a two-dimensional plane requires a complex pattern of contraction and relaxation in numerous muscles. Multiple agonist and antagonist muscles on both sides must receive appropriate signals to ensure a smooth, coordinated movement. Unfortunately, a simple recording technique does not exist for quantifying these complex skeletal muscle responses. These factors have hindered the mapping of connections between the labyrinthine receptors and individual skeletal muscles and have limited our understanding of the cellular basis for the vestibular contribution to postural reflexes.

Vestibulospinal pathways

Secondary vestibular neurons influence spinal anterior horn cell activity by means of three major pathways: (1) the lateral vestibulospinal tract, (2) the medial vestibulospinal tract, and (3) the reticulospinal tract. The first two arise directly from neurons in the vestibular nuclei, but the third arises from neurons in the reticular formation that are influenced by vestibular stimulation (as well as several other kinds of input). The cerebellum is highly interrelated with each of these pathways.

Lateral vestibulospinal tract

It is generally agreed that the vast majority of fibers in the lateral vestibulospinal tract originate from neurons in the lateral vestibular nucleus (Fig. 144-20) (Brodal, 1974). A somatotopic pattern of projections originates in the lateral vestibular nucleus such that neurons in the rostral ventral region supply the cervical cord, whereas neurons in the dorsocaudal region innervate the lumbosacral cord. Neurons in the intermediate region supply the thoracic cord.

In the spinal cord the fibers run ipsilaterally in the ventral half of the lateral funicle and the lateral part of the ventral funicle. The tract terminates throughout the length of the cord in the eighth lamina and the medial part of the seventh lamina, either directly on dendrites of anterior horn cells or on interneurons that project to anterior horn cells of the axial and proximal limb musculature (Nyberg-Hansen, 1964a). Some of the cells of the eighth lamina send their axons to the contralateral cord, probably accounting for the bilateral effects that have been observed with stimulation of the lateral vestibular nucleus. Activation of the vestibulospinal fibers by electric stimulation in the lateral nucleus produces monosynaptic excitation of extensor motor neurons and disynaptic inhibition of flexor motor neurons (Erulkar et al, 1966; Lund and Pompeiano, 1965). Both alpha and gamma motor neurons of extensor muscles receive monosynaptic, excitatory postsynaptic potentials (EPSPs). Gamma motor neurons fire at lower magnitudes of stimulation, however, so that muscle spindles are activated before stronger stimulation evokes alpha discharge and muscle contraction (Gernandt, 1974). The gamma system appears to function as a sensitizing device, ensuring smooth continuous control, whereas the alpha system provides a rapid forceful contraction. Consistent with this interpretation is the fact that interrupting the gamma loop by cutting the dorsal roots only slightly reduces the tension that vestibular stimulation produces in the gastrocnemius muscle (Gernandt, 1974).

Medial vestibulospinal tract

The fibers of the medial vestibulospinal tract originate from neurons in the medial vestibular nucleus and enter the spinal cord in the descending MLF (see Fig. 144-20) (Brodal, 1974). The fibers travel in the ventral funicle as far as the midthoracic level. The majority end on interneurons in the seventh and eighth laminae of the cervical cord (Nyberg-Hansen, 1964b). No monosynaptic connections appear to exist between the medial vestibulospinal tract and cervical anterior horn cells (Gernandt, 1974; Wilson et al, 1968).

Functionally, the medial vestibulospinal tract plays an important part in the interaction of neck and vestibuloocular reflexes. It has far fewer fibers than either the lateral vestibulospinal or reticulospinal tracts. Long-latency excitatory and inhibitory postsynaptic potentials have been recorded intracellularly from both flexor and extensor cervical motor neurons after stimulation of the descending MLF (Wilson et al, 1968).

Reticulospinal tract

The reticulospinal tract originates from neurons in the bulbar reticular formation (Peterson, 1984). The nuclei reticularis gigantocellularis and pontis caudalis provide most of the long fibers passing into the spinal cord, although the majority of neurons in the caudal

reticular formation also contribute fibers. Both crossed and uncrossed fibers traverse the length of the spinal cord, terminating in the seventh and eighth laminae of the gray matter (Nyberg-Hansen, 1965).

Stimulation of the pontomedullary reticular formation in the regions where the long descending spinal projections originate results in an inhibition of both extensor and flexor motor neurons throughout the spinal cord (Llinás and Terzuolo, 1964, 1965). If localized electrical stimulation is applied to the more rostral or lateral regions of the reticular formation, facilitation is produced rather than inhibition (Terzuolo et al, 1965). This facilitory influence must involve multisynaptic connections, because the neurons in these regions have short axons and do not send fibers into the spinal cord. The inhibitory and facilitory reticulospinal fibers do not form well-defined tracts within the spinal cord, although some separation of inhibitory and facilitory fibers occurs in the lateral funicle. As in the case of the lateral vestibulospinal tract, both alpha and gamma neurons are influenced by excitatory and inhibitory input from the reticulospinal tract.

The vestibular nuclei are only one of many structures that send fibers to the reticular formation. Axonal branches and collaterals of cells in all four main vestibular nuclei are distributed to the pontomedullary reticular formation. Only a small number of primary vestibular fibers end in the reticular formation, so that the main vestibular influence on reticulospinal outflow is mediated by way of the secondary vestibular neurons. A pattern exists within the vestibulo-reticular projections such that each nucleus projects to different areas of the reticular formation, but no detailed somatotopic organization has been identified (Brodal, 1974).

Cerebellar-vestibular pathways

The "spinal" cerebellum provides a major source of input to neurons whose axons form the lateral vestibulospinal and reticulospinal tracts. A somatotopic organization of projections to the lateral nucleus occurs in both the vermian cortex and the fastigial nuclei (Brodal, 1967; Pompeiano, 1974; Roberts, 1967). Direct projections connect the vermian cortex to the lateral vestibular nucleus, and indirect projections pass through the fastigial nuclei. The caudal part of the fastigial nucleus gives rise to a bundle of fibers that cross the midline (Russell's hook bundle), curving around the brachium conjunctivum before running to the contralateral lateral vestibular nucleus and dorsal lateral reticular formation. In addition, direct ipsilateral outflow passes from the fastigial nucleus to areas of the reticular formation that send long fibers to the spinal cord in the reticulospinal tract. The cerebellar-reticular pathways do not exhibit somatotopic organization (Pompeiano, 1974).

The cerebellar vermis and fastigial nuclei receive input from secondary vestibular neurons, the spinal cord, and the pontomedullary reticular formation. The result is a close-knit vestibular-reticular-cerebellar functional unit for the maintenance of equilibrium and locomotion.

Neural mechanisms of vestibulospinal reflexes

Studies of secondary vestibular neurons identified as part of the vestibulospinal pathways are few compared to those of neurons that are part of the vestibuloocular pathways.

Duensing and Schaefer (1959) identified four types of second-order otolith units based on their response to ipsilateral and contralateral tilts. Alpha neurons increased their firing rate with ipsilateral tilts and decreased their rate with contralateral tilts. Beta neurons showed the opposite response. Gamma and delta neurons increased and decreased their discharge, respectively, regardless of the direction of head tilt. The great majority of the units were of the alpha or beta type (alpha units twice as common as beta units). Adrian (1943) first demonstrated that second-order otolith units that were activated by static head tilt were also activated by linear horizontal acceleration of the head in the opposite direction. Melvill Jones and Milsum (1970) studied the dynamic response of otolith units during sinusoidal linear horizontal acceleration in the cat. They found that the phase of these units relative to head acceleration varied with frequency, being in phase with head acceleration at very low frequencies but in phase with head position at high frequencies. Clearly, these secondary neurons were integrating information from otolith afferents and other sites. Peterson et al (1980) studied the dynamic response of secondary vestibular neurons projecting to the spinal cord via the lateral vestibulospinal tract by applying sinusoidal polarizing currents to electrodes implanted close to the horizontal or anterior semicircular canal ampulae in decerebrate cats. They compared the activity in these secondary neurons with that of neck muscle EMG. These secondary vestibulospinal neurons exhibited a range of behaviors with some leading the applied stimulating waveform while others lagged the applied stimulating wafeform similar to the EMG activity recorded in the neck muscles. In other words, some of these units were in phase with head position rather than velocity, indicating that an integration of the peripheral afferent signal must have occurred at the level of the vestibular nuclei just as it has been demonstrated to occur within the vestibuloocular reflex.

Motor Responses

Canal-ocular reflexes

The semicircular canal-ocular reflexes produce eye movements that compensate for head rotations. Angular head rotations of small amplitude within the frequency range of natural head movements (1 to 4 Hz) result in compensatory sinusoidal eye movements 180 degrees out of phase with the head. If the stimulus to the semicircular canals is of large magnitude - one that cannot be compensated for by the motion of the eye in the orbit - the slow vestibular-induced eye deviation is interrupted with quick movement in the opposite direction. Although the eye movement during the slow component takes place in different locations in the orbit, gaze stabilization is still possible because the eye velocity during the slow component is approximately equal and opposite to that of the head. Because of the resetting fast components, the trajectory of the eye motion during the slow components effectively compensates for the head rotation, as if the eye had unlimited freedom of motion.

Pattern of eye motion

Intuitively, one might assume that the slow phases of nystagmus deviate the eyes toward the periphery of the orbit and that the fast components reset them to the center. Indeed, this pattern occurs in rabbits. In animals with more developed visual oculomotor function, however, the fast components act as anticipatory movements, taking the eyes toward the periphery (Melvill Jones, 1964). The fast components of the initial beats of nystagmus are larger than the preceding slow components, and the eyes deviate in the direction of the fast

component. In the human being, the exact threshold position varies with the velocity of the slow component of nystagmus, but it is usually near the midposition (Honrubia et al, 1977).

Characteristics of induced eye movements

Fig. 144-21 illustrates the nystagmus responses of a normal human subject to the three basic types of angular acceleration described earlier. The subject was rotated in the plane of the horizontal semicircular canals with the eyes open in complete darkness while performing continuous mental arithmetic to maintain alertness. Each stimulus produced a peak angular velocity of 120 degrees/sec. The slow component velocity profiles (Fig. 144-21, right side) for each stimulus can be predicted by the pendulum model. Note the similarity between these profiles and the time course of cupular deviation illustrated in Fig. 144-6. An important feature not addressed by the simple pendulum model is the adaptation phenomenon. The impulse response best illustrates the effect of adaptation on induced nystagmus. Instead of slowly returning to the baseline as would be predicted by the pendulum model, the velocity of the slow component reverses direction and then slowly returns to the baseline (as shown in Fig. 144-21, D). Reversals of this type consistently occur in normal subjects when the step change in angular velocity is greater than 100 degrees/sec (Sills et al, 1978).

The *gain* of the eye movement response is traditionally defined as the peak slow-phase eye velocity divided by the peak stimulus velocity. The *time constant* of the impulse response is defined as the time required for the response to decay to 1/e or to 37° of the maximum value. For sinusoidal tests the *phase* is typically measured by comparing the time of the maximum head velocity with the time of the maximum slow-phase eye velocity. Consistent with the pendulum model, the maximum slow-phase eye velocity leads the maximum head velocity at low frequencies of sinusoidal rotation in normal subjects (although the amount of phase lead at low frequencies is less than that predicted by the pendulum model because of the velocity storage mechanism described earlier). The time constant (Tvor) of the canal ocular reflex measured from a step change in angular velocity is inversely related to the phase lead (Ø) at low frequencies of sinusoidal rotation by

$$\mathbf{Tvor = 1 / w \tan Ø}$$

where w = 2 pi F.

Otolith ocular reflexes

Eye movements produced by head tilt

Compensatory eye movements produced by static head tilt in different animals are either rotational or torsional, depending on the direction of tilt and the position of the orbits in the skull. In rabbits and fish, lateral tilt causes a vertically directed rotational movement, and forward-backward tilt causes a torsional eye movement. In humans, compensatory torsional movements are produced by lateral tilt (ocular counterrolling), and vertical rotation results from backward-forward tilt. Eye movements associated with static tilt have been studied extensively in the rabbit. Head tilt in the dark within a range of ¡Ó 45 degrees about the normal position causes a compensatory eye deviation with a gain of approximately 0.6 (Baarsma and Collewijn, 1975). That is, the angle of eye rotation is approximately 60% of

the angle of tilt. In human subjects the ocular response to tilt is much less efficient. The maximum ocular torsion for a lateral tilt of 50 degrees is only 5 or 6 degrees (a gain of approximately 0.1) (Miller, 1962).

Eye movements produced by linear acceleration

Continuous linear acceleration in a vehicle along a straight track theoretically constitutes an ideal stimulus to test the function of the otolith ocular reflex. The direction of the linear acceleration vector lies perpendicular to the earth's vertical axis, and the effective stimulus is the result of interaction of the force as a result of the vehicle's acceleration with that of gravity. Unfortunately, from a clinical point of view, the length of a track required to produce measurable otolith-ocular reflex is much greater than is feasible.

Niven and co-workers (1965) used a linear track to produce periodic linear acceleration in human subjects at different frequencies and in different head orientations. Linear acceleration along the interaural axis induced compensatory horizontal eye movements (including nystagmus), but acceleration in the head-foot axis (lying) or occipital nasal axis (sitting) did not induce vertical eye movements. The horizontal eye movements induced by linear acceleration in the interaural axis were about the same whether the subjects were lying or sitting. The magnitude and phase of the horizontal nystagmus induced by linear acceleration (so-called L-nystagmus) were different from those associated with periodic angular acceleration of the canals in a comparable frequency range, so it is unlikely that the result is from unanticipated stimulation of the horizontal canals. Buizza and associates (1980) also produced horizontal L-nystagmus in seated normal subjects during horizontal acceleration along the interaural axis in the dark.

The parallel swing is a device for presenting linear acceleration in a relatively small space. It is a platform suspended fro the ceiling by four stiff bars about 2 to 3 m in length. The oscillation amplitude and hence the acceleration depend on the initial deviation of the platform, which, once released, exhibits a damped oscillation with a frequency dependent on the length of the supporting bars. The parallel swing has a vertical as well as a horizontal displacement, although the former is small if the amplitude is small.

Eye movements induced in a normal human subject sitting on a parallel swing in the dark are shown in Fig. 144-22 (Baloh et al, 1988). Displacement along the interaural axis (upper three traces) produces sinusoidal horizontal eye movements with occasional corrective fast components. Vertical eye movements are approximately sinusoidal with a frequency twice that of the swing consistent with the fact that the small vertical displacement occurs at twice the swing frequency. When subjects sat facing forward so that the linear acceleration occurred in the occipital nasal axis, almost identical vertical but no consistent horizontal eye movements were induced (lower three traces). The fact that the horizontal and vertical eye movements were directly related to the magnitude of the horizontal and vertical linear acceleration, respectively, indicates that the brain must be able to distinguish between gravity and other linear acceleration components of the otolith signal. This is reasonable from a functional point of view, since the logical function of the reflex is to augment visual pursuit during linear displacement of the head (analogous to the role of the canal ocular reflex during angular displacement of the head). For example, lateral head movements require horizontal, not torsional, eye movements to maintain fixation on an earth-fixed target. How this

distinction is achieved at the cellular level is yet to be determined.

Canal otolith interaction

Most natural head movements are composed of a combination of linear and angular displacements so that the canal and otolith ocular reflexes must work together to assure steady fixation. There is an important difference, however, between the geometry of target displacement with angular and linear accelerations. With the latter, the angle of the required compensatory eye movement increases as the target moves closer to the subject. Buizza and colleagues (1981) proposed a model of canal otolith ocular reflex interaction that assumes that the gain of the canal ocular reflex is fixed while that of the otolith ocular reflex increases with decreasing target displacement. Their simple model ignores interocular spacing and the separation of the vestibular organs from the eyes (that is, it assumes a central cyclopean eye), but this is not a major problem as long as the target distance is greater than 1 m. With this model, if the head rotates with angular velocity a and translates with linear velocity t, then the eye angular velocity w - -a - kt, where k inversely depends on target distance. Virre and associates (1986) recently showed that the magnitude of induced eye movements measured in monkeys during combined linear and angular accelerations (by varying the radius of head rotation) was dependent on target location. Further, they observed that the adjustments occurred too fast (within 10 msec) to be visually guided. They proposed that the ocular system makes use of a rapid, nonvisual estimate of current target location relative to the head by combining available visual, auditory, and proprioceptive information.

The velocity storage feedback pathways within the central VOR (see Fig. 144-13) provide a key mechanism for otolith canal interactions (Cohen et al, 1983; Raphan and Cohen, 1985). This can best be illustrated by the response of a monkey to off vertical axis rotation (OVAR) (Fig. 144-23). If the animal is rotated at a constant velocity about a tilted vertical axis, the slow-phase velocity of induced nystagmus does not decay to zero (as when the monkey is vertical) but rather persists at a steady state level. If the animal is suddenly stopped, postrotatory nystagmus after OVAR is much less than when the animal is stopped in the upright position (in Fig. 144-23, compare b and c with a). Blocking the semicircular canals does not alter the steady state response during OVAR, indicating that the otoliths generate the signals necessary for continuous nystagmus. It has been postulated that sequential excitation and inhibition of the otolith hair cells by the rotating gravity vector produces a traveling wave, the velocity of which is estimated centrally and then passed on to the velocity storage integrator, which produces the continuous horizontal nystagmus (Raphan and Cohen, 1985). Velocity storage can be activated by many types of stimuli (canal, otolith, vision), and through a three-dimensional gravity-dependent structure the system is capable of storing information to produce eye movements in all planes (Cohen and Henn, 1988).

Neck-vestibular interactions

Since the time of Bárány (1907), rotating the body with the head stationary and measuring the eye movements has been considered a potential functional test of the human neck ocular reflex pathways (Barlow and Freeman, 1980; Barnes and Forbat, 1979). Several methodological problems have been encountered, however. It is difficult to induce body motion and concurrently maintain the head completely stationary so as to avoid vestibular stimulation. As with vestibular-induced eye movements care must be taken to inhibit fixation

while monitoring the neck-induced eye movement. Even if these problems are overcome, a body torsion of 50 to 60 degrees results in a compensatory eye deviation of only 4 to 5 degrees (Meiry, 1971). The magnitude of the reflex response varies with the frequency of sinusoidal body rotation, being optimal at 0.1 and 1 Hz (when eye and body motion are in phase) (Takemori and Suzuki, 1971). Compensatory sinusoidal eye movements induced by sinusoidal body rotation take on the appearance of nystagmus if the stimulus is large enough. The direction of the slow phase of nystagmus is such that the eye is driven in phase with the motion of the trunk.

The neck ocular reflexes exert influence on both vestibular and optokinetic nystagmus. Tonic neck deviation in the rabbit produces an imbalance in an otherwise symmetric nystagmus that results from rotating the animal sinusoidally with the head and body normally aligned. When the slow components of nystagmus are in the direction of the neck-induced tonic ocular deviation, the amplitude of fast components and the velocity of the slow components are smaller than those of nystagmus in the opposite direction.

Visual-vestibular interactions

Organization of visually controlled eye movements

Visual motion information reaches the oculomotor neurons via two pathways: a direct pathway with fast dynamics and an indirect pathway with slower dynamics (Fig. 144-24) (Cohen et al, 1981). A key feature of the indirect pathway is the velocity storage element shared with the vestibuloocular reflex. Optokinetic stimulation activates both pathways, whereas pursuit activates only the direct pathway (Robinson, 1981). The velocity storage element accounts for the slow buildup in optokinetic nystagmus (OKN) and for optokinetic afternystagmus (OKAN). The direct pathway accounts for the initial rapid rise in OKN and the rapid drop after turning off the lights.

In 1936 Ter Braak performed a series of experiments in which he confirmed the presence of cortical and subcortical optokinetic pathways in several animal species. Cortical OKN was elicited by movement of a series of relatively small objects that attracted the animal's attention (so-called active nystagmus), and subcortical OKN was produced by movement of the whole optical environment (passive nystagmus). Presumably, the cortical pathway corresponds to the direct (pursuit) pathway and the subcortical pathway to the indirect (velocity storage) pathway. In animals without a fovea, such as the rabbit, only passive OKN can be induced, and bilateral occipital lobectomy produces a minimal effect on induced OKN (Hobbelen and Collewijn, 1971). In cats and dogs, passive and active OKN can be induced, but only the latter is abolished by bilateral occipital lobectomy (Ter Braak et al, 1971). In monkeys, bilateral occipital lobectomy abolishes smooth pursuit and the initial rapid rise in OKN (leaving the slow buildup in OKN intact), but after a few months the animals regain some smooth pursuit and part of the rapid phase of OKN (Zee et al, 1987).

Since human subjects have poor OKAN and do not exhibit a buildup in OKN slow-phase velocity, the subcortical (indirect) pathway must be less prominent in humans than in other animals. It has been a general clinical dictum that patients with cortical blindness do not produce OKN. Ter Braak and associates (1971), however, reported a patient with cortical blindness caused by infarction of the occipital lobes and lateral geniculate nuclei who

exhibited a slow buildup of OKN in one direction only. This interesting patient denied seeing any movement despite the presence of OKN. Patients with lesions of the parietal lobe and midline cerebellum also exhibit a slow buildup in OKN; presumably the indirect pathway is uncovered after loss of the direct pathway (Baloh et al, 1980, 1986).

Visual-vestibular eye movements

Fig. 144-25 gives a simple linear interaction model for the visual and vestibuloocular systems (Raphan and Cohen, 1985). The two independent block diagrams in Fig. 144-13, B, and Fig. 144-24 have been interrelated to produce a single-output eye velocity. When the target (foveal or full field) is stationary, movement of the head results in an equivalent movement of the target in the opposite direction relative to the head. When both the target and the head move, the driving stimulus to the visual motor system is the angular velocity of the target relative to the head; that is, the difference between the target velocity relative to space and the head angular velocity relative to space. In the absence of head movement, the eye movement response is under the control of the closed-loop visual motor system; whereas if the head is rotated in the dark, the visual system is inoperative and the eye movement response is under the control of the vestibular system.

A quantitative assessment of this model is beyond the scope of this chapter, but a few general features deserve emphasis because of their relevance in clinical testing. A full-field target activates both the direct (pursuit) and the indirect (velocity storage) pathways, the latter shared with the vestibular system. OKAN provides the only independent measure of the indirect pathway. A foveal target, on the other hand, activates predominantly the direct pathway (pursuit afterresponses are minimal) (Lisberger et al, 1981). Therefore pursuit testing is almost exclusively a measure of the direct visual motor pathway.

For both systems, gain of induced eye movements depends on the velocity and frequency of the stimulus. The visual motor system is most efficient at low target velocities and frequencies. Normal human subjects can track a target moving sinusoidally at 0.1 Hz, peak velocity 30 degrees/sec with a gain near 1. The gain rapidly falls off for target velocities greater than 100 degrees/sec and frequencies greater than 1 Hz. By contrast, the gain of the vestibuloocular reflex is about 0.6 when a human subject is sinusoidally rotated in the dark at 0.1 Hz and a maximum velocity of 30 degrees/sec. Unlike the visual motor system, however, the vestibuloocular reflex response has a gain near 1 for frequencies from 1 to 4 Hz and velocities greater than 100 degrees/sec. The reader can test the increased efficiency of the vestibular system over the visual motor system at high-input velocities and frequencies by a simple maneuver: rapidly move your hand back and forth with increasing velocity with your head stationary until your hand appears blurred. Then hold your hand stationary and move your head back and forth at the same high speed. Despite the rapid head movement the smallest detail of the palm remains clear (Melvill Jones, 1985).

At low-input frequencies and velocities (head or target), the gain of the direct visual motor pathway is an order of magnitude higher than that of the other pathways. This explains why normal subjects can almost completely inhibit the VOR when rotated with a fixation target at the low frequencies commonly used for clinical testing (that is, less than 0.1 Hz). On the other hand, at high-input frequencies and velocities the gain of the VOR is near 1 while the gain of the visual motor system rapidly falls off. Therefore at these high frequencies

and velocities there is relatively little fixation suppression of the VOR.

Postural reflexes

The elementary unit for the control of tone in the trunk and extremity skeletal muscles is the myotatic reflex (the deep tendon reflex). The myotatic reflexes of the antigravity muscles are under the combined excitatory and inhibitory influence of multiple supraspinal neural centers (Bard, 1961). At least in the cat, one finds two main facilitory centers (the lateral vestibular nucleus and the rostral reticular formation) and four inhibitory centers (the pericruciate cortex, basal ganglia, cerebellum, and caudal reticular formation). The balance of input from these different centers determines the degree of tone in the antigravity muscles. If one removes the inhibitory influence of the frontal cortex and basal ganglia by sectioning the animal's midbrain, a characteristic state of contraction in the antigravity muscles results - so-called decerebrate rigidity. The extensor muscles increase their resistance to lengthening, and the deep tendon reflexes become hyperactive. One may conclude that the vestibular system contributes largely to this increased extensor tone after witnessing the marked decrease on bilateral destruction of the labyrinths (Bach and Magoun, 1947). Unilateral destruction of the labyrinth or the lateral vestibular nucleus results in an ipsilateral decrease in tone, indicating that the main excitatory input to the anterior horn cells arises from the ipsilateral lateral vestibulospinal tract (Fulton et al, 1930).

Tonic labyrinthine reflexes

In a decerebrate animal with normal labyrinths the intensity of the extensor tone can be modulated in a specific way by changing the position of the head in space (Magnus, 1924; Sherrington, 1906). The tone is maximal when the animal is in the supine position with the angle of the mouth 45 degrees above the horizontal and minimal when the animal is prone with the angle of the mouth 45 degrees below the horizontal. Intermediate positions of rotation of the animal's body about the transverse or longitudinal axis result in intermediate degrees of extensor tone. If the head of the upright animal is tilted upward (without neck extension), extensor tone in the forelegs increases; downward tilting of the head causes decreased extensor tone and flexion of the forelegs. Lateral tilt produces extension of the extremities on the opposite side. These tonic labyrinthine reflexes, mediated by way of the otoliths, seldom occur in intact animals or human subjects because of the inhibitory influence of the higher cortical and subcortical centers. They can be demonstrated in premature infants, however, and in adults with lesions releasing the brain stem from the higher neural centers (McNally and Stuart, 1967).

Vestibulocolic reflexes

Analogous to the vestibuloocular reflex the function of the vestibulocolic reflex (VCR) is to maintain head position in space when the head is unexpectedly moved. In fact, these two reflexes normally work synergistically to extend the dynamic range of ocular stability. When animals lower on the phylogenetic scale undergo angular acceleration in a plane of the horizontal semicircular canal with the head free to move they develop combined eye and head nystagmus with both reflexes contributing approximately equally to overall gaze stabilization. The horizontal VCR depends only on the horizontal semicircular canals, whereas rotations about the pitch plane activate both semicircular canals and otoliths. Disynaptic connections

between the vestibular nerve and neck motor neurons have been identified bilaterally (Wilson and Yoshida, 1969), and the pattern of disynaptic excitation and inhibition between individual ampullary nerve branches and dorsal neck motor neurons is consistent with the reflex movements expected in response to natural activation of the semicircular canals (Wilson and Maeda, 1974).

As suggested earlier, the vestibuloocular reflex (VOR) must control only a pair of agonist and antagonist muscles, whereas the VCR must control a large number of neck muscles that move the head. Peterson et al (1985) identified 15 muscles (on each side) that act on the head or first cervical vertebra in the cat. They measured the origins and insertions of each of these muscles stereotactically and identified a direction of torque exerted by each muscle about a particular point by calculating the product of vectors extending from the muscle insertion to its origin and from the muscle insertion to the joint. They concluded that the coordinate frame of the neck motor system is nonorthogonal; that is, the muscles do not produce movements along directions that lie at right angles to one another. Further, the coordinate system is overcomplete since 30 muscles (15 on each side) are acting to control 6 or 7 degrees of freedom of joint rotation that underlie normal head movements. Therefore there is no single pattern of muscle activity that corresponds to each head position, but rather there are an infinite number of patterns of muscle activity for any given head position.

In an attempt to determine how the brain determines the motor pattern in generating the VCR, Baker et al (1985) rotated decerebrate cats in numerous different planes while recording electromyographic (EMG) activity in seven neck muscles. They found that each muscle had an optimal activation direction that was consistent across animals. In other words, there was a single solution from among the infinite number of possible motor patterns that could be used to generate the VCR. Pellionisz and Peterson (1988) used tensor network theory to develop a model of the VCR that predicted the activation directions of the different muscles with a reasonable degree of accuracy. Understandably, studies of the neural processes involved in generating the VCR lag behind studies of the VOR.

Adaptive Mechanisms

Response to vestibular lesions

Much of our knowledge of labyrinthine function was accumulated at the turn of the century from clinical and experimental observations in humans and animals with unilateral and bilateral lesions of the peripheral labyrinth (Breuer, 1874; Ewald, 1892; Magnus, 1924). At that time a controversy existed concerning whether the symptoms associated with loss of labyrinthine function were caused by irritation or paralysis of the effected labyrinth. The subsequent discovery of the continuous flow of action potentials in the unstimulated vestibular nerve led to the present concept that symptoms are usually caused by an imbalance of the normal resting activity, that is, by a unilateral decrease in activity.

The magnitude of symptoms and signs following labyrinthine lesions depends on (1) whether the lesion is unilateral or bilateral, (2) the rapidity with which the functional loss occurs, and (3) the extent of the lesion. Simultaneous removal of both labyrinths in most experimental animals does not produce severe abnormalities at rest, although vestibular reflex activity is lost and ocular and postural stability is impaired. Similarly, patients who have

slowly lost vestibular function bilaterally (for example, secondary to streptomycin treatment) may not complain of any symptoms referable to the vestibular loss. If closely questioned, however, they report visual blurring or oscillopsia with head movements and instability when walking at night (caused by loss of vestibuloocular and vestibulospinal reflex activity, respectively).

Unilateral acute labyrinthectomy, in contrast, results in severe symptoms and signs. Lower mammals are initially unable to walk and develop head torsion toward the affected side and decreased ipsilateral extensor muscle tone. Nystagmus is prominent, with a slow component directed toward the damaged side and a fast component toward the intact side. These signs abate with time but may persist for months after surgery.

A sudden unilateral loss of labyrinthine function in humans is a dramatic event. Patients complain of severe dizziness and nausea, they are pale and perspire, and they usually vomit repeatedly. They prefer to lie motionless but can walk if forced to (deviating toward the side of the lesion). Neck torsion and changes in extremity tone are minimal. A brisk, spontaneous nystagmus interferes with vision. These symptoms and signs are temporary, and the process of compensation starts almost immediately. Within 1 month, most patients return to work with few, if any, residual symptoms. If the patient slowly loses vestibular function unilaterally over a period of months or years (for example, with an acoustic neuroma), symptoms and signs may be absent.

Mechanism of compensation after labyrinthectomy

Knowledge of the different types of secondary vestibular neurons and their interconnecting pathways (see Fig. 144-12) is important for understanding the sequence of recovery following a unilateral loss of labyrinthine function (Precht et al, 1966). Immediately after labyrinthectomy the ipsilateral type 1 neurons lose their spontaneous activity and become unresponsive to ipsilateral angular rotation. At the same time, contralateral healthy type 1 neurons lose their inhibitory contralateral input, and their spontaneous activity increases in comparison to normal (Precht and Dieringer, 1985). Contralateral type 2 neurons lose their inputs from excitatory type 1 neurons and cannot be identified electrophysiologically. An imbalance in the tone of body and eye musculature results, and clinical signs of labyrinthectomy are produced: nystagmus, past pointing, and imbalance. A few days after a labyrinthectomy, the previously silent type 1 neurons on the damaged side recover their spontaneous activity and begin to recover their response to physiologic stimulation of the contralateral labyrinth (Ried et al, 1984; Sirkin et al, 1984; Yagi and Markham, 1984). As a result of their connections with ipsilateral type 2 neurons, these reactivated type 1 units are inhibited when the type 1 neurons on the healthy side are excited and disinhibited when the contralateral type 1 neurons are inhibited. Although the responses of the type 1 neurons on the damaged side are not as intense as those on the normal side, they are qualitatively similar. The recovery of sensitivity in ipsilateral type 1 neurons after a labyrinthectomy paralells the time course of improvement in clinical symptoms and signs.

The genesis of the renewed tonic input to ipsilateral type 1 neurons several days after a complete labyrinthectomy is not really known (Lacom and Xerri, 1984). It does not come from the healthy side, because afferent activity on that side does not change (Precht et al, 1966). It might result from sprouting of axons from other sources (for example,

somatosensory, visual, or commissural inputs) or from an increased efficacy of the remaining intact synapses (Gacek et al, 1988). In animal studies the course of compensation is affected by exercise (Igarashi et al, 1981), visual experience (Fetter et al, 1988), and drugs (as a rule, stimulants accelerate and sedatives slow compensation) (Lacom and Xerri, 1984). If a second labyrinthectomy is performed after compensation for the first occurs, the animal again develops signs of acute unilateral vestibular loss with nystagmus directed toward the previously operated ear (Bechterew's compensatory nystagmus), as if the first labyrinthectomy had not taken place. Compensation after the second labyrinthectomy is slightly faster than the first but still requires several days.

Changes in VOR after unilateral vestibular lesions

Patients who suddenly lose vestibular function on one side have asymmetric responses to rotational stimuli because of (1) a DC bias resulting from the spontaneous nystagmus and (2) the difference in response to ampullopetal and ampullofugal stimulation of the remaining intact labyrinth (Baloh et al, 1977). These features are readily seen in the sinusoidal rotational data shown in Fig. 144-26. The patient was tested shortly after the acute onset of vertigo caused by a right peripheral vestibular lesion (probable viral neurolabyrinthitis). At the time of testing, he exhibited a spontaneous left beating nystagmus (eyes open in the dark) with an average slow-phase velocity of 10 degrees/sec. This spontaneous nystagmus added to rotational-induced nystagmus in the same direction and subtracted from that in the opposite direction. The effects of this DC bias and of the asymmetry in response to ampullopetal and ampullofugal stimulation of the intact labyrinth are best illustrated in the plot of eye velocity versus stimulus velocity (Fig. 144-26, B, right side). The DC bias (the eye velocity at the point of the Y intercept) is equivalent to the average slow-phase velocity of the spontaneous nystagmus. The gain (slope) of the response with ampullopetal stimulation of the intact labyrinth is twice that with ampullofugal stimulation.

With compensation the DC bias gradually disappears and the gain asymmetry between ampullopetal and ampullofugal stimulation decreases but does not disappear. It remains most pronounced after high-intensity stimuli. Patients with compensated unilateral peripheral vestibular lesions show a characteristic pattern of decreased gain and increased phase lead at low frequencies of sinusoidal stimulation. These changes appear to be fixed in that they can be observed as long as 10 years after an acute unilateral peripheral loss (Jenkins et al, 1982; Wolfe et al, 1982). Their functional implications are minimal, however, inasmuch as the visual motor system can compensate for the loss of vestibular function in the low-frequency range.

Adaptive modification of vestibuloocular reflex with vision

Although clinicians have long been aware of the adaptive changes that occur within the VOR after lesions, quantitative assessment of these capabilities in normal subjects has only recently been undertaken. Based on the psychophysical studies of Kohler (1962), Gonshor and Melvill Jones (1971, 1976a, 1976b) began a series of experimental studies designed to investigate the potential for adaptive plasticity within the VOR. Probably the most remarkable example of this plasticity was the complete reversal of the VOR that occurred in normal subjects after wearing optically reversing prisms. After about 2 weeks of wearing goggles that produce continuous left-right reversal of the visual environment, the VOR

measured in the dark adaptively changed such that the direction of the slow and quick phases of induced nystagmus was the reverse of normal. The process occurred gradually over days, initially with a drop in gain, followed by a progressive change in phase (although never quite reaching the desired 180-degree phase shift). After the goggles were removed, the VOR gradually returned to normal somewhat faster than the original adaptation. Subsequent studies using magnifying and minifying lenses in normal humans (Melvill Jones, 1985) and a variety of animals (Mandl et al, 1981; Miles et al, 1980; Robinson, 1976; Wallman et al, 1982) showed that a dark-measured VOR gain could be increased and decreased, almost with a machinelike precision. Further, these adaptive changes were not restricted to a single plane. For example, if an animal was sinusoidally rotated in one plane (the horizontal) while the visual surround was simultaneously rotated in another plane (the vertical), the VOR measured with horizontal rotation in the dark developed a vertical component (Schultheis and Robinson, 1981). Although the site of these induced plastic changes in the VOR remains uncertain, the cerebellum appears to play a key role. Lesions of the cerebellum in a variety of animals block adaptive plasticity of the VOR (Ito, 1975; Miles et al, 1981; Robinson, 1976). Recent work of Lisberger (1988) indicates that although the cerebellum provides a critical signal needed for the adaptive process, the modifiable synapse is probably on neurons within the vestibular nucleus.

Vestibular Contribution to Orientation

Vestibulocortical pathways

The first electrophysiologic identification of vestibulocortical projections was made in the cat by Watzl and Mountcastle (1949). Following electrical stimulation of the contralateral vestibular nerve, they recorded short latency monophasic potentials in the suprasylvian gyrus just anterior to the auditory area. The ascending vestibulocortical system includes at least three synaptic stations: the vestibular nuclei, the thalamus, and the cerebral cortex (Buttner-Ennever, 1981; Mergner et al, 1981). A large anterior vestibulothalamic projection runs ventrally in the brain stem, passing lateral to the red nucleus and dorsal to the subthalamic nucleus, to terminate in the main sensory nucleus of the thalamus. A smaller posterior vestibulothalamic projection runs in the lateral lemniscus along with the auditory projections and ends predominantly near the medial geniculate. The vast majority of vestibulothalamic projections run outside the MLF. Two separate thalamocortical projections areas have been identified in the monkey: one near the central sulcus close to the motor cortex, and the other at the lower end of the intraparietal sulcus next to the face area in the postcentral gyrus (Büttner and Lang, 1979; Fredrickson et al, 1974). In humans, electrical stimulation of the superior sylvian gyrus and the region of the inferior intraparietal sulcus produces a subjective sensation of rotation or body displacement (Penfield, 1957).

The vestibulocortical pathway via the thalamus is concerned with control of body position and orientation in space. Thalamic and cortical units that receive vestibular signals are also activated by proprioception and visual stimuli. Most units respond in a similar way to rotation in the dark, or to moving visual fields, indicating that they play a role in relaying information about self-motion. From a functional point of view, the vestibulothalamocortical projections appear to integrate vestibular, proprioceptive, and visual signals to provide one with a "conscious awareness" of body orientation.

Motion perception

Semicircular canals

If a subject is rotated about an earth-vertical axis on a rotatory platform, he will perceive turning that depends on the magnitude of angular acceleration. The perceived "speed of turning" progressively increases with prolonged constant acceleration, although the turning sensation increases at a lesser rate than platform velocity. Below a minimum or threshold angular acceleration, the subject does not perceive turning. Although considerable difference exists in reported values, the threshold to constant angular acceleration is in the range of 0.1 to 0.5 degrees/sec^2 (Clark, 1967; Guedrey, 1974). This is approximately an order of magnitude lower than the constant angular acceleration necessary to produce nystagmus.

Attempts to correlate the threshold and magnitude of subjective sensation with the magnitude of angular acceleration represent the earliest clinical tests of vestibular function. Cupulometry developed by Van Egmond and associates (1949) is still occasionally used for assessing vestibular function on the basis of subjective sensation. With this test the subject is maintained at a constant velocity of angular rotation and then suddenly stopped. The durations of “after-turning” sensation are measured for impulses of different amplitude (usually 15 to 60 degrees/sec) and plotted versus the log of impulse magnitude (in the so-called cupulogram). The intercept of the line with the abscissa corresponds to a subjective sensation threshold; and the slope, a time constant of after-turning sensation. Normative data for the subjective threshold vary from 1 to 4 degrees/sec, and the time constant of after-turning sensation varies from 2 to 14 seconds (Jongkees and Groen, 1946).

Otolith organs

A subject undergoing horizontal linear oscillation (for example, on a parallel swing) reports experiencing two separate types of motion. One is a sensation of linear movement in the horizontal plane, and the other is a sensation of tilt. Both sensations vary with the changing velocity (acceleration) of the platform (Jongkees and Groen, 1946). Beginning with low amplitudes of oscillation, the subject initially perceives motion without a specific direction. This is followed by perception of the direction of linear movement and finally at higher intensities of stimulation by a perception of tilting. Using dynamic stimuli, estimates of the minimal horizontal linear acceleration that normal subjects can perceive range from 5 to 15 cm/sec2 (Guedry,1974).

The most complete data on threshold and accuracy of estimation of tilt have been obtained with static tilt experiments (Clark, 1970; Graybiel, 1974). The subject is strapped to a tilt platform in darkness and is asked either to estimate the deviation of his head from the earth-vertical or to adjust a luminous line on a dark field to a vertical position. Normal subjects respond with an accuracy of 2 to 4 degrees of tilt angles up to 40 degrees (accuracy falls off progressively for larger angles of tilt) (Bauermeister,1964; Graybiel, 1974). The subjective estimate of tilt obviously depends on the gravitational force (Ormsby and Young, 1976). If the subject is asked to estimate the angle of tilt under different gravitational forces, the estimate will vary with Fg (see Fig. 144-5, A). For g values less than 1 the angle of tilt is underestimated, whereas for g values greater than 1 the angle of tilt is overestimated. In experiments carried out at zero gravity in parabolic

aircraft flights and in orbiting spacecraft, the subjects are unable to perceive tilt.

Visual-vestibular conflicts

Motion-sickness

Motion sickness refers to the syndrome of dizziness, perspiration, nausea, vomiting, increased salivation, yawning, and generalized malaise induced by motion (Johnson and Jongkees, 1974; Money, 1970). It is usually produced by vestibular stimulation but also can be induced by visual stimulation (for example, with prolonged optokinetic stimulation). Both linear head acceleration and angular head acceleration induce motion sickness if applied for long periods in susceptible subjects. Combinations of linear and angular acceleration or multiplane angular accelerations are particularly effective. Rotation about the vertical axis, along with voluntary or involuntary nodding movements in the sagittal plane, rapidly produce motion sickness in nearly all subjects. This movement combines linear and angular acceleration (Coriolis effect).

Autonomic symptoms are usually the first manifestation of motion sickness. Sensitive sweat detectors can identify increased sweating as soon as 5 seconds after onset of motion, and grossly detectable sweating is usually apparent before any noticeable nausea. Increased salivation and frequent swallowing movements occur early. Gastric motility is reduced, and digestion is impaired. Hyperventilation is almost always present, and the resulting hypocapnia leads to changes in blood volume with pooling in the lower extremities, predisposing the subject to postural hypotension. Motion sickness affects the appetite so that even the sight or smell of food is distressing.

Some people are sensitive to the development of motion sickness, but others are highly resistant. Most will adapt to prolonged vestibular stimulation, but some never adapt. Unfortunately, there is no reliable way to predict who will develop motion sickness. Thresholds for vestibular stimulation (rotational or caloric) and the rate of habituation to vestibular stimulation are no different in susceptible and resistant subjects (DeWitt, 1953; Jongkees, 1974). Patients whose labyrinths have been inactivated by congenital or acquired disease are resistant to motion sickness, whether induced by visual or vestibular stimuli. Such patients can withstand prolonged exposure to wave motion during a heavy storm at sea that would lead to motion sickness in even the most hardened seafarers.

Motion sickness seems to result from a visual-vestibular conflict (Money, 1970). This theory is supported by the fact that visual influences during body motion have a clear effect on the development of motion sickness. The symptoms are aggravated if one sits in an enclosed cabin on a ship or in the back seat of a moving vehicle. Because the environment is moving with the subject, visual-vestibular conflict occurs. The vestibular system signals movement, while the visual system signals a stationary environment. Motion sickness can be alleviated by improving the match between visual and vestibular signals. This can be accomplished on a ship by standing on the deck and focusing on the distant horizon or on land, if possible. When riding in a car, the susceptible subject should sit in the front seat to allow ample peripheral vision of the stationary surround. Motion sickness suppressants such as scopolamine and dimenhydrinate are effective presumably by diminishing activity at the vestibular nucleus and thereby diminishing the potential for

visual vestibular conflict (Wood, 1990).

Space sickness

Space sickness is a kind of motion sickness that is induced by active head movements in space (Lackner and Graybiel, 1986; Olman et al, 1986). It has occurred in approximately 50% of astronauts and cosmonauts who have entered space. Most adapt within 2 to 3 days. Because active head movements do not elicit motion sickness within the gravitational conditions on earth the absence of gravity appears to be a key factor. The leading theory at present is that the symptoms are generated by a mismatch between the otoliths and semicircular canals as well as between otolith and visual signals (Lackner and Graybiel, 1986). On earth the semicircular canals and otoliths work together, sensing the angular and linear acceleration components of active head movements, but in space the otoliths fail to signal orientation in the absence of gravity. Thus the afferent signals generated by head movements in space are different from the signals from prior calibration on earth. The vestibular system must recalibrate to account for the absence of gravity; presumably this recalibration takes about 3 days. Supporting this notion, some astronauts develop transient motion sickness when they return to earth, although it is usually of shorter duration than in space.