Mini-Review

Development of the Gravity Sensing System

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The utricle and saccule contain hair cells, which are the peripheral sensors of change in gravity that transmit signals regarding these changes to the neural components of the vestibular system. Although the fundamental neural pathways, especially the vestibular reflex pathways, have been investigated extensively, the principals underlying the functional development of this system are under study at present. The objective of this review is to identify the gravity-sensing components of the vestibular system and to present an overview of the research performed on their development. The second part of this review is focused on one important aspect of development, the emergence of electrical excitability using the chick tangential vestibular nucleus as a model. The importance of this research to understanding vestibular compensation and vestibular disturbance during spaceflight is considered. Because there is a conservation of the fundamental pathways and function in vertebrate phylogeny from birds through mammals, findings from studies on avians should contribute significantly to understanding the mechanisms operating in mammals. Also, we expect that as the events and basic mechanisms underlying normal vestibular development are revealed, these will provide practical tools to investigate the pattern of recovery from dysfunction of the vestibular system. This is related to the evidence suggesting that recovery of function in different systems and cell lines, including neurons, involves repeating certain patterns established during development. J. Neurosci. Res. 63:103–108, 2001.
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Classically, the term "gravity-sensing organs" refers to the utricle and saccule, the peripheral parts of the vestibular system that detect and process vestibular stimuli evoked by changes in gravity. The present definition, however, has been expanded to identify a system, with peripheral and central components, that is involved in processing signals related to detecting gravity changes. The revised definition results from a redirection of research from investigating primarily peripheral vestibular endorgans to include studies of the brain where plasticity underlying vestibular compensation is thought to reside. To understand what happens under conditions producing vestibular dysfunction, it is necessary to define the normal structure and function of the vestibular system, and developmental studies help to achieve this goal. Here, we focus

on characterizing the development of electrical excitability in vestibular nuclei neurons and raise the possibility that developmental events and their underlying mechanisms may be repeated during recovery from certain pathologies of the vestibular system, including the vestibular disturbances encountered on exposure to altered gravitational environment during spaceflight. This laboratory has utilized the chick vestibular system to study both development and vestibular compensation after peripheral vestibular nerve lesions, so this review will focus on the findings from this morphologically simple vestibular circuit.

BASIC CHARACTERISTICS OF THE VESTIBULAR SYSTEM[1]

Structure of the Gravity-Sensitive Components

In response to movements of the head or changes in gravity, a major role of the peripheral vestibular endorgans is to alert the brain of these events so that muscles are activated to produce movements of the body and eyes to aid the organism in maintaining appropriate posture and balance. The peripheral vestibular endorgans are situated in the inner ear and contain two distinct types of sensors. The three semicircular canals contain hair cells responding to rotational movements, or angular acceleration, whereas the utricle and saccule contain hair cells detecting changes in gravity, or linear acceleration.

In the vestibular system, the basic structures whose development may depend in part on exposure to gravitational stimuli include: a) hair cells of the utricle and saccule, b) vestibular ganglion cells that form synapses with these hair cells peripherally and vestibular nuclei neurons centrally, c) vestibular nuclei neurons themselves, and d) motor neurons receiving input from vestibular nuclei neurons. The axons of vestibular nuclei neurons compose the

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vestibular reflex pathways, which represent the main tracts of the vestibular system participating in the control of posture, movements and balance. The three major pathways include the vestibulo-ocular tracts controlling eye movements used to maintain visual gaze, the vestibulocollic tracts innervating the neck muscles used to support the head, and the vestibulospinal tracts innervating the muscles of the upper and lower extremities used to maintain posture and balance. The morphology of the central vestibular pathways, connections, and development has been studied most extensively within the last 15 years (e.g., Glover and Pettursdottir, 1988; Cox and Peusner, 1990a).

The gravity-driven otoliths produce basic postural adjustments by interacting with signals from the semicircular canals in the vestibular nuclei (e.g., Dickman and Fang, 1996). The vestibular nuclei, however, are not simple relay centers for processing peripheral vestibular signals, but act as sites for convergence of multiple sensory inputs. Other sensory systems known to interact with the vestibular system primarily at the level of the vestibular nuclei include the proprioceptive system, involved in controlling muscle length and tension (e.g., Sato et al., 1997), and the visual system, concerned with controlling eye movements (e.g., Wylie et al., 1997). Little is know about the exact nature of these interactions within the vestibular nuclei and virtually nothing is known about their development.

Conscious awareness or the perception of motion and spatial orientation are thought to arise through convergence of signals from vestibular, visual, and somatosensory systems at the thalamocortical level (e.g., Shiroyama et al., 1999). The vestibular nuclei project to the ventral posterior nuclei of the thalamus, where electrical stimulation of this part of the thalamus can produce sensations of movement or dizziness. Cerebral cortical areas involved in producing movements, spinning, or dizziness on electrical stimulation in humans include parietal lobe cortex near the intraparietal sulcus and postcentral sulcus, and the cortical area at the base of the central sulcus next to motor cortex (e.g., Brandt and Dieterich, 1999). The development of the connections of these areas has not been investigated.

There has accumulated evidence of vestibular system involvement in regulating the autonomic nervous system. For example, the vestibular system may influence cardiovascular output (Yates and Miller, 1994) and pulmonary function (Miller et al., 1995). Moreover, during exposure to microgravity unloading the otolith receptors can result in disturbances in autonomic function. The pathways subserving vestibular autonomic connections are complex and not fully established, either structurally or functionally, and how these connections develop is not known.

Vertebrate brains form and maintain multiple neural maps of the spatial environment, that provide distinctive topographical representations of the different sensory and motor systems. For example, visual space is mapped onto the retina in a two-dimension coordinate plan (Sperry, 1944). This plan is then remapped in several places with the central nervous system (CNS), including the superior colliculus (Gaze and Jacobson, 1963), the lateral geniculate nucleus and the visual cortex (Hubel and Wiesel, 1970). Besides visual maps, the localization of sound in space is mapped throughout the central ascending auditory pathway from cochlear nuclei to auditory cortex (Olsen et al., 1989). Also, the hippocampus has an important topographical map because it functions in providing short-term memory for an animal's location in a specific spatial position (e.g., Teng and Squire, 1999). In mature animals, neural maps must be synchronized so that appropriate perceptual and motor adjustments are made. A well-studied example is the ability of the owl to localize sound in space. The owl can change its gaze to the source of a sound in space, since the animal maintains auditory and visual maps of space in register within the optic tectum (Rucci et al., 1997). This system of neural space maps must have information on the location of the head in the gravitational field. Accordingly, the vestibular system must play an important role in maintaining and organizing these maps. During development, all of these maps must be established, and they must be plastic because realignment must occur as the animal grows.

Role of Sensory Stimulation During Ontogeny

The vestibular system is a sensory–motor integrating system. In every other sensory system studied, sensory stimulation has been found to play a critical role in the initial specification of the connections and physiological properties of the constituent neurons. In the visual system, visual activity in the retinal pathway influences the specification of the connections determining how visual information is processed in the cerebral cortex (for review, see Penn and Shatz, 1999). Only in the otolithic gravitational pathway has it been impossible to investigate the role of sensory deprivation, because there is no simple way to deprive the system of gravitational stimulation on Earth. Accordingly, experiments should be performed in space to test the hypothesis that gravity itself plays a role on the development and maintenance of the neural components of the peripheral and central vestibular system.

It is important to distinguish between overstimulation and understimulation, or sensory deprivation, as factors that perturb a system. In the auditory system, overstimulation can produce wholesale destruction of the sensory receptor cells and a toxic condition in neurons, known as excitotoxicity, that may result from an overaccumulation of excitatory neurotransmitters, such as glutamate (e.g., Kim et al., 1997). For example, this can induce catastrophic changes in calcium fluxes and cell death (e.g., Zirpel and Rubel, 1996). In the auditory system, tinnitus, or ringing in the ears, may represent a persistent state of hyperactivity in the CNS (Attias et al., 1996). The neurological effects of understimulation or sensory deprivation, however, are relatively minor in adult animals, producing some atrophy of neuronal cell bodies but seldom neuron death in the CNS (Powell and Erulkar, 1962). In contrast to adult animals, the effects of sensory deprivation in infants or embryos can result in neuron death in the CNS and seriously disrupt the establishment of connections (e.g., Peusner and Morest, 1977a). In consideration of these observations made on the vestibular and other

sensory systems, it is critical to study how microgravity, that probably represents decreased stimulation of the vestibular system, affects the developing vestibular neural pathway. Further, it can be implied from studying other sensory systems that the mechanisms activated in hypergravity are unlikely to resemble those operating in microgravity.

Major Developmental Events

In the CNS, neurons usually undergo a set sequence of major events in their ontogeny, regardless of the type of neuron to be formed. The major events include *proliferation* of neuron precursors in the ventricular zone, *migration* of precursors to their definitive location, that is typically lateral or external to the site of proliferation, and *differentiation,* that includes dendritic outgrowth, synapse formation, and the emergence of signal processing and spontaneous activity. These events occur in the development of vestibular nuclei neurons (e.g., Peusner and Morest, 1977b; Peusner and Giaume, 1997) and it is important to learn what role sensory stimulation plays on them.

When the otocyst is ablated in young chick embryos, before the primary vestibular fiber enter the CNS at 3 embryonic days (E3), neurons in the CNS migrate and begin to differentiate by growing out axons and dendrites, but require contact by the primary vestibular fibers to continue their differentiation and survive (Peusner and Morest, 1977a; Petralia et al., 1991). From experiments performed mainly on the rat, but also on the chick vestibular system, it is known that the PNS develops in advance of the CNS. The sequence of events in synapse formation by first-order vestibular neurons were studied rather uniquely in the chick. These are all bipolar ganglion cells, some of which give rise to large-diameter primary vestibular fibers, the colossal fibers that form extremely large calycine endings both centrally and peripherally. Due to these natural labels, it was determined from rapid Golgi preparations that these large vestibular calyces developed 2 days in advance of the large calyces within the tangential nucleus in the brain (Fink and Morest, 1977). In addition to this, a developmental gradient has been found among vestibular nuclei neurons. For example, at birth neurons in the rat lateral vestibular nucleus involved in postural stabilization have matured, yet neurons in the superior and medial nuclei functioning in gaze stabilization do not mature until 2 weeks later (Clarac et al., 1998).

Signal Processing

To understand functional development, it is necessary first to characterize the mature pattern of activity, that provides an endpoint to determine how far along in development the neurons have progressed. Concerning mature vestibular nuclei neurons, one important feature is the presence of spontaneous activity, that has been observed in many sensory neurons (Hoagland, 1932). Spontaneous activity is related to the membrane and ionic properties of the cell and can result in the spontaneous discharge of action potentials or a transient depolarization or hyperpolarization. Spontaneous firing rates vary among different animal species and among different sensory systems. In vestibular nuclei neurons, spontaneous activity is thought to play a key role in allowing them to respond to high frequency synaptic stimuli (du Lac and Lisberger, 1995) and encode information by modulating the spontaneous firing rate. For instance, the discharge rate for primary vestibular fibers is relatively high and constant, at about 70 to 90 spikes/sec in the monkey (e.g., Baloh and Honrubia, 1993). A second important feature of mature vestibular nuclei neurons is that most of them fire action potentials tonically. This means that these neurons generate spikes for the duration of the stimulus. Indeed, these two properties of spontaneous activity and tonic firing are essential for most mature vestibular nuclei neurons to transmit faithfully the temporal characteristics of vestibular stimuli and for normal reflex function.

Development of Firing Pattern

There are few developmental studies of excitability in vestibular nuclei neurons. Most of them have been performed on rodents in which vestibular maturation occurs rather late during the first postnatal month (Lannou et al., 1979; Dutia et al., 1995; Johnston and Dutia, 1996). In this research, all of the vestibular nuclei neurons studied exhibited a period of phasic firing before the emergence of a tonic firing pattern and spontaneous spiking activity. In our study performed with intracellular recordings, the same developmental transition from phasic to tonic firing reported in mammals was found to occur in chick embryos, but at earlier ages and in a more compressed schedule (Peusner and Giaume, 1997). Thus, in contrast to rodents, the development of the chick vestibular system occurs rapidly during embryonic stages, because within hours after birth the chick must stand and initiate vestibular-controlled head movements necessary to its survival.

DEVELOPING CHICK AS A MODEL TO STUDY VESTIBULAR DYSFUNCTION

Structure of the Chick Tangential Nucleus and Firing Pattern of its Principal Cells

Studies on the electrical excitability of second-order vestibular nuclei neurons have been performed in this laboratory using the chick tangential nucleus as a model (Fig. 1). Based on its synaptic cytoarchitecture (Sotelo and Palay, 1970) and connections (Cox and Peusner, 1990a,b), the tangential nucleus closely resembles the mammalian lateral vestibular nucleus, although its oculomotor connections are similar to those characterizing some neurons of the mammalian medial vestibular nucleus. The predominant neuron class consists of the principal cells (80%), a group of neurons with a unique structure. They receive synapses from the spoon endings, that are very large terminals formed en passant by the largest-diameter primary vestibular afferents, the colossal fibers. Their size and shape are striking in the light microscope and uniquely identify these structures. The tangential nucleus receives a topographic input from the ampullary nerves, including both small and large diameter fibers, in addition to input from the
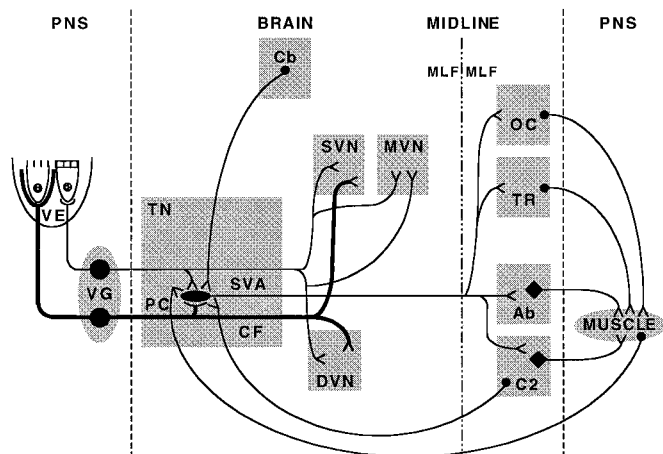
Fig. 1. Connections of the tangential nucleus (TN), a vestibular nucleus in the brainstem composed of vestibulo-ocular-collic neurons representative of gravity-sensing neurons that participate in the vestibular reflex pathways. VE, vestibular epithelium; VG, vestibular ganglion; PC, principal cell; EC, elongate cell; CF, colossal fiber; SVA, small vestibular fiber; SVN, MVN, and DVN, superior, medial and descending vestibular nuclei; MLF, medial longitudinal fasciculus; OC, TR and AB, oculomotor, trochlear and abducens nuclei; C2, cervical spinal cord; CNS, central nervous system; PNS, peripheral nervous system.
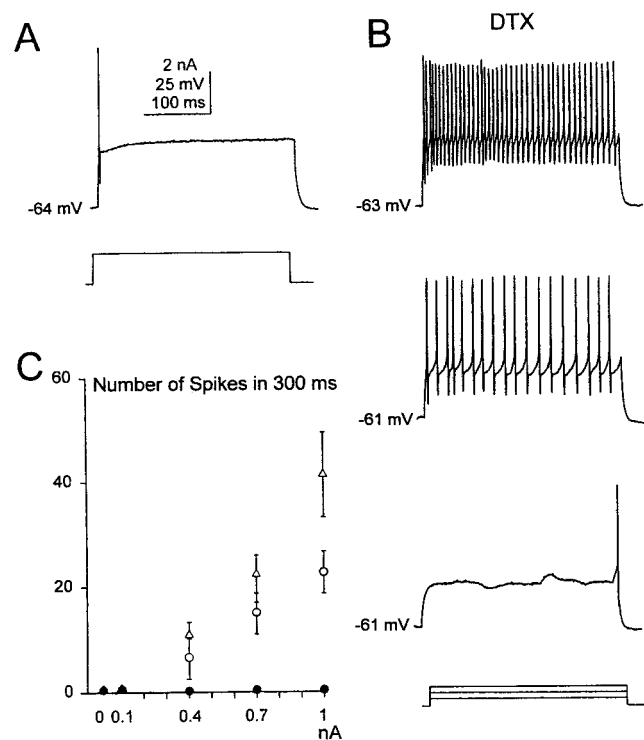

Fig. 2. Dendrotoxin (DTX) transforms accommodating principal cells into neurons firing trains of spikes in E16 chick embryos. **A:** Current-clamp recordings of an accommodating principal cell before and after (**B**) exposure to 200 nM DTX in normal ACSF. **C:** Plot of the number of spikes in 300 msec vs. injected current amplitude for accommodating (●), firing (○), and accommodating principal cells after exposure to DTX (△). Adapted from Gamkrelidze et al. (1998).

cerebellar flocculus, cervical spinal cord, and hatching muscle. Principal cell axons project to neurons in the oculomotor, trochlear and abducens nuclei, and also to cervical spinal cord. Accordingly, the principal cells are vestibulo-ocular-collic neurons that participate in two of the three vestibular reflexes. The development of the firing pattern in principal cells was investigated at three critical ages for the development of spoon endings: E13 and E16, and 1–2 days after hatching (H1-2) (for review, see Peusner, 1992). At E13, all of the principal cells recorded fired one spike and accommodated, regardless of how much current was injected. E16 represented a turning point, when only a few principal cells could fire multiple action potentials on depolarization, and most cells generated one spike and then accommodated. Finally, at H1-2, the vast majority of the principal cells fired repetitively on depolarization, as expected from mature second-order vestibular nuclei neurons (Peusner and Giaume, 1997). Thus, during development the principal cells of the chick tangential nucleus seem to gradually acquire the ability to generate non-accommodating firing of action potentials.

Role of Potassium Currents

In the central auditory pathway, potassium currents play an essential role in determining whether various nuclei neurons fire trains of action potentials or accommodate. Accordingly, to understand the mechanisms underlying the developmental changes in excitability observed in vestibular nuclei neurons, we analyzed the outward potassium currents and investigated their role in accommodation (Gamkrelidze et al., 1998, 2000).

First, we studied brain slices of the chick tangential nucleus in E16 chicks using infrared imaging and Nomarski optic to identify the recorded neurons. The principal cells exhibited both transient and sustained potassium currents. The low-threshold dendrotoxin-sensitive sustained potassium current (I_{DS}) was associated with the principal cells that fired one spike and accommodated on depolarization and was not expressed in those neurons that fired repetitively on depolarization at E16. Blocking I_{DS} transformed accommodating principal cells into neurons capable of firing trains of action potentials on depolarization (Fig. 2). Therefore, the suppression of I_{DS} during this embryonic age is sufficient to transform accommodating vestibular nuclei neurons into non-accommodating firing neurons and suggests that developmental regulation of this current may be necessary for the establishment of normal vestibular function. In hatchlings, the vast majority of principal cells fire repetitively in response to depolarization (Peusner and Giaume, 1997) and whole-cell recordings (Gamkrelidze et al., 2000) indicate that I_{DS} contributes significantly less to the total current than found in E16 chick embryos.

Neuroplasticity

Neuroplasticity refers to the long-lived changes in structure and function that both developing and mature

neurons may exhibit due to changes in their activity. The degree of plasticity observed depends in part on the age of the animal, with younger animals more sensitive to change (Levi-Montalcini, 1949), the type of lesion or kind of change (Li et al., 1995), and the time during neural development that the change occurs (i.e., whether the change occurs during a critical developmental period) (e.g., Knudsen et al., 1984). The magnitude of neural alterations encountered may be gross, microscopic or molecular, involving cell death (Peusner and Morest, 1977a), cell atrophy (Powell and Erulkar, 1962), loss of dendrites (Sanes, 1992), synaptic reorganization (Jean-Baptise and Morest, 1975), LTP (long-term potentiation) (e.g., Malenka and Nicoll, 1999), LTD (long-term depression) (e.g., Caillard et al., 1999), or change in synaptic efficacy (e.g., Lissin et al., 1999). Neuroplasticity is important to characterize because it may result in functional change not only in the target neuron, but within the entire pathway or system in which the target neuron participates (e.g., Killackey et al., 1994). Thus, synaptic changes at the cellular level can result in profound changes within the entire organism and can influence behavior.

Normal function of the vestibular reflexes requires that both vestibular labyrinths are intact, as the brain processes vestibular signals by comparing those received from both ears. Should an imbalance in inputs occur, however, an important type of plasticity is exhibited by the central vestibular system, called vestibular compensation. In cases of permanent dysfunction caused by unilateral labyrinthectomy or vestibular nerve lesion, all vertebrate brains, including humans, exhibit rapid recovery from most of the static symptoms in about a week (e.g., Smith and Curthoys, 1988a,b). The neurological symptoms include dysequilibrium, disorientation, and locomotor effects, all of which diminish or disappear in most adult mammals and birds. Vestibular compensation most likely involves CNS changes, because after labyrinthectomy the vestibular nerve does not function (Igarashi et al., 1970) and the vestibular nuclei must be intact for compensation to occur (Dieringer et al., 1984). It is interesting that in the medial vestibular nucleus (MVN) in the intact guinea pig, extracellular recordings performed 0–8 hr after labyrinthectomy showed that neurons on the ipsilateral side lose their spontaneous activity, whereas contralateral MVN neurons exhibited increased spontaneous activity (Smith and Curthoys, 1988a,b). Neurons on both sides recovered their normal resting activity 52–60 hr after surgery. The decreased spontaneous spiking activity in the ipsilateral MVN may be due to averaging firing rates of silent neurons with others having normal resting discharges (Ris et al., 1995, 1997). The natural abatement of vestibular symptoms occurring in vivo after peripheral vestibular lesion could be explained by changes in spontaneous spiking activity. Moreover, the intrinsic membrane properties of vestibular nuclei neurons should be investigated as well, because changes in ionic channels have been observed in various cells subjected to injury or disease (e.g., motor neurons; Iwahashi et al., 1994; glial cells; MacFarlane and Sontheimer, 1997).

The principal cells of the chick tangential nucleus offer an established model to study vestibular compensation, because light and ultrastructural observations already have been correlated with behavioral testing in whole animals (Aldrich and Peusner, 1992). Briefly, after unilateral vestibular ganglionectomy performed on young hatchlings, vestibular compensation occurred in three stages: 0–3 days, large vestibular synapses degenerated and severe behavioral deficits were observed; 4–9 days, the central processes of the primary vestibular fibers degenerated and marked improvements were apparent in both static and dynamic symptoms; 19–56 days, the neuroanatomical features were stable and the dynamic symptoms improved gradually but never disappeared. Thus, following unilateral ganglionectomy vestibular compensation occurred in the chick in the absence of new synapses on the tangential principal cell bodies. This suggests that other changes, perhaps in membrane properties, underlie the observed behavioral changes. Finally, during and after spaceflight, astronauts experience vestibular disturbances that mimic the symptoms observed in subjects with pathological changes in the neurovestibular system. Accordingly, it is relevant to spaceflight to investigate the mechanisms of vestibular compensation on Earth.

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