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Introduction

# Vestibular compensation: New clinical and basic science perspectives

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## 1. Introduction

This symposium on vestibular compensation was held in Baltimore, Maryland, on February 16, 2009, at the 32nd annual midwinter research meeting of the Association for Research in Otolaryngology. The meeting program and abstracts have been published online (http://aro.org/abstracts/abstracts.html). The articles, which underwent peer-review for this special issue, address different aspects of vestibular compensation, with the objective of covering a wide spectrum of topics rather than focusing on one approach. Thus, both clinical and basic science studies are presented. The roles of the vestibular nuclei, other brainstem nuclei, vestibular inner ear, cerebellum, and spinal cord in vestibular compensation are discussed. The experiments apply a wide range of approaches, from testing the subject's balance on stationary and moving platforms to recording vestibulo-ocular reflex (VOR) activity and extracellular single units in intact animals, and whole-cell patch-clamp recordings in brain slices. The presentations emphasize new perspectives on patient diagnosis, treatment, and the basic mechanisms underlying vestibular compensation. We would like to thank the Journal of Vestibular Research for this special issue devoted to this symposium.

## 2. Overview

In all vertebrates, the peripheral vestibular system operates as a bilateral network continually signaling the brain concerning changes in the position of the head in space, while the brain processes these signals by comparing the inputs received from the two ears. Damage to the peripheral vestibular system on one side can precipitate a complex and debilitating syndrome of oculomotor and postural deficits. Vestibular neuritis [1], Meniere's disease [4], vestibular schwannoma [12], and benign paroxysmal positional vertigo [21] represent peripheral vestibular pathologies that can result in unilateral vestibular dysfunction [7]. Patients with these pathologies experience labyrinth dysfunctions that may be partial or complete, fluctuating or constant, progressive or recovering. Gentamicin injection or vestibular neurectomy to treat Meniere's disease, as well as vestibular ganglionectomy to treat vestibular schwannoma, lead to permanent and irreversible loss of vestibular function on the operated side. The symptoms of the lesions are diverse, including vertigo, nystagmus, head and body tilt, ataxia, imbalance, nausea and vomiting. Altogether, the symptoms can be separated into static symptoms which occur at rest and usually recover within about a week after the lesion, and dynamic symptoms which appear during movements and take considerably longer to compensate, if at all. Many consequences of these lesions diminish or disappear rapidly due to an adaptive process called "vestibular compensation". Although the basic phenomenon of vestibular compensation has been known since the classical studies of Bechterew [2], and investigated intensely over the last 40 years, identifying the neural correlates and sequence of events underlying the behavioral recovery require

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further investigation. Nonetheless, studies on the recovery of function after vestibular deafferentation provide an advantageous model for understanding brain adaptation to lesions because behavioral testing can be performed during the recovery. In most cases, the patients recover on schedule after a one-sided peripheral vestibular lesion, but symptoms in some patients do not compensate and the patients experience persistent disequilibrium, vertigo, and ataxia [7].

Since the vestibular receptors do not regenerate, and the vestibular nuclei must be intact for behavioral recovery to occur [14,20], scientists realized early on that compensation must involve extensive rewiring of the remaining vestibular circuitry. During normal function, first- and second-order vestibular neurons usually generate spontaneous spike discharge at rest, which produces a net output that is symmetric bilaterally. Spontaneous spike discharge from the primary vestibular fibers provides a major source of tonic input to the vestibular nuclei neurons. In primates, there are about 20,000 primary vestibular fibers [9], with a resting spike discharge rate in the range of 80–100 spikes/sec [10]. Thus, the challenges imposed on the central nervous system (CNS) after unilateral loss of vestibular function are profound. Acute dysfunction of one labyrinth will produce marked asymmetry in the remaining inputs to the vestibular nuclei neurons on the lesion side compared to the intact side. The asymmetry in the spontaneous spike firing of primary vestibular fibers bilaterally is related causally to the onset of symptoms [18,19], and behavioral recovery from the static symptoms largely coincides with restoring the symmetric spontaneous spike activity in vestibular nuclei bilaterally, although some disparity exists [15,16]. Thus, vestibular compensation is thought to result from CNS readjustments that restore accuracy and symmetry to the vestibular pathways and reflexes that normally depend on information from the vestibular labyrinths [6]. Potential inputs contributing to the changes in vestibular nuclei neurons after vestibular deafferentation include those originating from the spinal cord [23], cerebellum [5, 13,23], intact portions of the peripheral vestibular system [5], viscera [23], and contralateral vestibular nuclei through the inhibitory commissural pathways [13].

Finally, in cases where both labyrinths are removed simultaneously, the subjects exhibit ataxia, spatial disorientation, and oscillopsia, but fail to show the oculomotor and postural symptoms characteristic of unilateral vestibular lesions [3]. However, in cases where unilateral labyrinthectomy is followed by partial or complete compensation, and then lesion of the remaining intact labyrinth, the subjects show the symptoms observed after unilateral vestibular deafferentation, which altogether is known as the "Bechterew phenomenon" [2,8].

## 3. Designing appropriate test equipment for patients with vestibular deficits

An important aspect of treating patients with vestibular lesions is to design appropriate equipment for detecting and measuring their balance deficits. This task requires an assessment of the gross anatomical structures and their interactions which maintain balance under normal conditions, and their aberrations after vestibular lesions. These experiments have been performed primarily using quadruped animal models. Vidal et al. [22] identify multiple factors which make quadrupeds suitable for determining how bipeds achieve appropriate balance, despite the former's lack of the improved sense of balance characteristic of species with upright posture. The article also describes the greater effectiveness of the moving compared to static platforms for testing posture control in vestibular lesion patients. Finally, the Authors discuss experiments that show that patients with vestibular lesions exhibit long-term deficits in posture control for side-to-side tilting in the roll plane, as found in quadruped animal models.

## 4. Recovery of VOR after unilateral vestibular deafferentation

From experiments performed on the squirrel monkey, Minor and Lasker [11] report that the symmetry of the horizontal VOR evoked by low frequency rotations is restored shortly after vestibular deafferentation, but no compensation occurs for the high frequency head rotations. After high frequency head rotations, only low amplitude responses are recorded for excitatory head rotations for the horizontal canal on the lesion side, while excitatory head rotations for the horizontal canal on the intact side are indistinguishable from the normal response. The article goes on to describe experiments performed on normal animals, animals subjected to unilateral plugging of the three semicircular canals, and adaptation to magnifying and minimizing spectacles. Finally, the Authors use their experimental data to design a mathematical model to better understand the role of regular and irregular primary vestibu-

lar fibers on the recovery of function after vestibular deafferentation.

The article by Cullen et al. [5] reviews a series of neurophysiological studies directed toward understanding the neural mechanisms underlying vestibular compensation in alert behaving animals. The Authors characterize VOR dynamics in two important animal models, the rhesus monkey and mouse, applying stimuli over a physiologically relevant range of head movements before and after vestibular deafferentation. From the rhesus monkey studies, evidence is presented to support the idea that vestibular compensation involves changes in the intact peripheral vestibular system, including vestibular nerve afferents and efferents, and produces more phasic primary vestibular afferent response dynamics. Finally, the Authors describe recent experiments that show that although vestibular compensation is limited in the cerebellar-deficient, Lurcher mutant mouse model, it is not lacking completely. Altogether, this work demonstrates that recovery of function after vestibular lesions results from adaptive changes within multiple sites that normally participate in vestibular signal processing, including the vestibular periphery, cerebellum, and noncerebellar central vestibular pathways.

## 5. Changes in nonlabyrinthine inputs of vestibular nuclei neurons after vestibular deafferentation

Yates and Miller [23] performed bilateral vestibular deafferentations to further understand the role of primary vestibular inputs in regulating postural stability and autonomic function during changes in posture. Although permanent loss of certain vestibular reflexes occurs after bilateral vestibular lesions, recovery of postural stability and cardiovascular responses related to posture takes place. Nonlabyrinthine inputs from diverse sources, including somatosensory, proprioceptive, and visceral inputs, undergo critical changes, which suggest that they compensate for vestibular signaling deficits. Specifically, from single unit recordings in the intact cat, caudal vestibular nuclei neurons (medial, inferior and lateral vestibular nuclei) regain spontaneous spike activity and discharge regularity within one week after bilateral vestibular deafferentation due to changes in non-labyrinthine inputs. The nonlabyrinthine inputs to the caudal vestibular nuclei neurons may be monosynaptic, but more often are multisynaptic, involving relay neurons. It is interesting that recovery of activity in the caudal vestibular nuclei neurons persists even after cutting the dorsal roots of the upper cervical spinal cord segments, but not after transecting the spinal cord at the first cervical level. Moreover, the cerebellar uvula must remain intact for recovery of cardiovascular responses during postural changes. Finally, the function of nonlabyrinthine inputs in modulating normal activity of caudal vestibular nuclei neurons is uncertain.

## 6. Electrophysiological recordings performed on brain slices

Most experiments conducted on vestibular nuclei in brain slice preparations have concentrated on neurons in the medial vestibular nucleus (MVN), the largest of the four main vestibular nuclei in the mammalian brainstem. However, the experiments presented by Shao et al. [17] follow three novel directions for characterizing the cellular and molecular changes in vestibular nuclei neurons after unilateral vestibular deafferentation. First, the work is performed on the chicken model, so it offers the opportunity to characterize recovery after vestibular lesions in bipeds. The chicken model is also unusual in that most vestibular-deafferented chickens, like humans, undergo a rapid process of compensation to the static symptoms in about a week, but other operated chickens fail to compensate, like some patients. Thus, the chicken model offers the opportunity to test what factors interfere with the recovery of function in some patients after unilateral vestibular deafferentation. These brain slice experiments focus on changes in sodium and potassium conductances, which are important for the emergence of spike firing pattern during development. Finally, the data are averaged from a single class of vestibular reflex projection neurons, the principal cells of the tangential vestibular nucleus, rather than recording from MVN neurons whose precise functional identity is unknown.

The article by Olabi et al. [13] discusses experiments that support a role for the GABAergic inhibitory commissural system, which interconnects the vestibular nuclei on both sides of the brain, in modulating vestibular nuclei neuron activity after vestibular deafferentation. The article also reports on the regulation of GABA release in vestibular nuclei neurons by histaminergic drugs, glucocorticoids, and neurosteroids.

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