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Integration of Nonlabyrinthine Inputs by the Vestibular System: Role in Compensation Following Bilateral Damage to the Inner Ear

Bill J. Yates¹ and Derek M. Miller²

¹Departments of Otolaryngology and Neuroscience, University of Pittsburgh, Pittsburgh, PA 15213

²Interdepartmental Neuroscience Program, Northwestern University, Chicago, IL 60611

Abstract

Inputs from the skin and muscles of the limbs and trunk as well as the viscera are relayed to the medial, inferior, and lateral vestibular nuclei. Vestibular nucleus neurons very quickly regain spontaneous activity following a bilateral vestibular neurectomy, presumably due to the presence of such nonlabyrinthine inputs. The firing of a small fraction of vestibular nucleus neurons in animals lacking labyrinthine inputs can be modulated by whole-body tilts; these responses are eliminated by a spinal transection, showing that they are predominantly elicited by inputs from the trunk and limbs. The ability to adjust blood distribution in the body and maintain stable blood pressure during movement is diminished following a bilateral vestibular neurectomy, but compensation occurs within a week. However, bilateral lesions of the caudal portions of the vestibular nuclei produce severe and long-lasting cardiovascular disturbances during postural alterations, suggesting that the presence of nonlabyrinthine signals to the vestibular nuclei is essential for compensation of posturally-related autonomic responses to occur. Despite these observations, the functional significance of nonlabyrinthine inputs to the central vestibular system remains unclear, either in modulating the processing of vestibular inputs or compensating for their loss.

Keywords

compensation; vestibulo-autonomic; balance; posture; cardiovascular; orthostatic hypotension

Although some responses produced by the vestibular system, including both the vestibulo-ocular [27] and vestibulo-collic reflexes [7], are permanently abolished following a bilateral vestibular neurectomy, postural stability [26] and posturally-related cardiovascular responses [10,12] recover over time. The latter findings emphasize the large role that nonlabyrinthine inputs may play in signaling body position in space. Mittelstaedt provided further evidence that inputs from the trunk, including visceral graviceptors, can contribute to a sense of spatial orientation [17]. As might be expected from these findings, somatosensory and proprioceptive signals have been shown to acquire a larger role in controlling postural stability in humans following the removal of vestibular inputs [15,20]. However, the neural mechanisms through which somatosensory inputs provide for compensation following loss of vestibular signals are yet to be deciphered. This review discusses evidence that labyrinthine and nonlabyrinthine inputs are integrated by the vestibular nuclei and cerebellum, such that somatosensory inputs can in part “substitute” for vestibular signals following damage to the inner ear.

Processing of somatosensory inputs by the vestibular nuclei

A number of studies have shown that vestibular nucleus neurons, particularly those located in the lateral, inferior, and caudal medial nuclei, integrate a variety of sensory inputs that reflect body position in space (e.g., [13,22,23,29,30]). For example, Figure 1 shows the fraction of vestibular nucleus neurons in decerebrate cats whose activity was modulated by stimulation of forelimb or hindlimb nerves containing muscle afferents [13]. Different shading patterns are used to indicate whether a neuron responded to nerve stimulation using low-threshold shocks (less than twice the threshold for eliciting an afferent volley) that likely only activated muscle spindle or Golgi tendon organ afferents or higher-threshold stimuli. The bottom panel of the figure provides data collected from labyrinth-intact animals, whereas the top portion shows responses from cats that received a bilateral labyrinthectomy approximately two months before the acute recording session was conducted. Although a majority of vestibular nucleus neurons responded to stimulation of limb nerves in labyrinth-intact animals, the fraction of cells receiving somatosensory inputs was significantly higher in animals that lacked vestibular signals. In particular, low-threshold inputs were more effective ($p < 0.001$, Fisher's exact test) in altering neuronal activity in labyrinthectomized animals [13]. As such, these data raise the possibility that nonlabyrinthine inputs to the vestibular nuclei are amplified following damage to the inner ear.

Anatomical studies have also demonstrated that relatively direct pathways exist to transmit somatosensory and visceral inputs to the vestibular nuclei. For example, a recent study compared the locations of neurons that were retrogradely labeled following the injection of a monosynaptic tracer (the β -subunit of cholera toxin) and a transneuronal tracer (pseudorabies virus) into the medial and inferior vestibular nuclei [11]. Injection of both tracers produced labeling of interneurons located along the entire length of the spinal cord, although the cells were 10 times more prevalent in the cervical cord than in the lumbar cord. Injections of either tracer also labeled neurons in all four vestibular nuclei, the prepositus hypoglossi, the reticular formation, the inferior olivary nucleus, the medullary raphe nuclei, the spinal and principal trigeminal nuclei, the facial nucleus, and the lateral reticular nucleus. However, the transneuronal tracer also labeled cells in additional areas following survival times that likely only permitted the viral agent to spread across two synapses, particularly in the nucleus tractus solitarius and the cuneate and gracile nuclei [11]. These data show that an anatomical substrate is present for somatosensory and visceral inputs to influence the activity of cells in the caudal regions of the vestibular nuclei, but suggest that these signals are primarily transmitted through relay neurons including those located in the brainstem reticular formation.

Effects of a bilateral labyrinthectomy on activity of vestibular nucleus neurons

Although an initial study suggested that spontaneous activity of vestibular nucleus neurons was depressed for a period following a bilateral vestibular neurectomy [24], more recent work showed that the firing of these neurons returns to pre-lesion levels within days after elimination of labyrinthine inputs [16,21]. For example, Figure 2 compares the rate and regularity of neuronal firing in the caudal regions of the vestibular nuclei of conscious cats determined before and during the first week subsequent to a bilateral vestibular neurectomy. No attempt was made to determine the number of silent cells that were present, and whether this number was lower in animals lacking vestibular inputs than in those with intact VIIIth nerves. Nonetheless, the firing frequency of spontaneously active cells after the removal of labyrinthine inputs (31 ± 4 (SEM) spikes/sec) was at least as high as when the vestibular nerves were intact (24 ± 1 spikes/sec) [16]. Firing regularity was also similar before and after elimination of labyrinthine signals; the coefficient of variation of firing rate was 0.8 prior to lesions and 0.9 afterwards [16]. It seems likely that the presence of nonlabyrinthine signals to the vestibular nuclei is essential

for maintaining a high level of electrical activity of neurons following the loss of signals from the inner ears.

In addition to retaining spontaneous activity following a bilateral vestibular neurectomy, some neurons in the caudal vestibular nuclei responded to moderate-amplitude tilts ($10\text{--}15^\circ$) of the whole body. This observation was first noted in recordings from decerebrate cats that were bilaterally labyrinthectomized approximately two months prior to the acute recording session [32]. In this preparation, the firing of 27% of neurons located in the vestibular nuclei was modulated by tilt. The responses persisted after the elimination of neck afferent inputs through a rhizotomy of the upper cervical dorsal roots. However, the activity of only one of 95 neurons was modulated by moderate amplitude whole-body tilts in animals that sustained both a chronic bilateral labyrinthectomy and a spinal transection at C2 [4]. These observations suggest that signals from spinal cord afferents are paramount in providing for responses of vestibular nucleus neurons to changes in body position in space following the loss of labyrinthine inputs.

Although the firing of a subset of vestibular nucleus units was modulated by whole-body rotations in animals lacking inputs from the inner ear, the spatial and dynamic properties of the responses of the neurons were considerably different than in labyrinth-intact animals. These response characteristics are illustrated in Figure 3. Within the relatively small population of neurons sampled, the plane of tilt that elicited the maximal response was typically within 25° of pitch in animals without vestibular inputs [32], but over two-thirds of vestibular nucleus neurons in labyrinth-intact animals had response vector orientations closer to the roll plane than the pitch plane [14,16]. The gain of responses of vestibular nucleus neurons sampled to pitch rotations in animals with a bilateral vestibular neurectomy was approximately 1 spike/s/ $^\circ$ across stimulus frequencies; the response phase was near stimulus position at low frequencies, and lagged position slightly at higher frequencies (average of $35\pm9^\circ$ at 0.5 Hz) [32]. While a subset of vestibular nucleus neurons recorded in vestibular-intact animals had similar response dynamics, the majority exhibited response gains that increased considerably as stimulus frequency was advanced, and had response phases near stimulus velocity at least when high-frequency rotations were delivered [14].

The responses of vestibular nucleus neurons to whole-body rotations have also been examined in conscious cats lacking vestibular inputs [16]. The response properties of the small subset of units whose activity was modulated by tilts were similar to those in decerebrate cats, as illustrated in Figure 3. However, the fraction of neurons that responded to moderate-amplitude rotations was lower in conscious animals than in decerebrates, and also varied between individuals. At most, the firing of 8% of cells in the areas of the vestibular nuclei studied was synchronized with 15° sinusoidal rotations of animals that had sustained a bilateral vestibular neurectomy [16]. Moderate-amplitude oscillations also affected the firing of a small fraction of neurons in the cerebellar fastigial nucleus of conscious cats lacking vestibular inputs: the activity of approximately 5% of fastigial nucleus units was modulated by 15° sinusoidal tilts in vertical planes. The responses of these neurons were similar to those of cells in the vestibular nuclei of animals lacking labyrinthine inputs, as illustrated in Figure 4. It remains to be determined, however, whether large-amplitude changes in body position would affect the firing of a greater proportion of vestibular nucleus or cerebellar neurons, permitting a crude discrimination of spatial location.

Comparison of compensation following central and peripheral vestibular lesions

In both decerebrate and conscious animals lacking labyrinthine inputs, most vestibular nucleus neurons whose activity was modulated by vertical rotations were preferentially activated by pitch tilts, despite the fact that few vestibular nucleus units responded best to pitch rotations

in labyrinth-intact cats. This observation, as well as the fact that the firing of only a small fraction of neurons was affected by whole-body rotations of moderate amplitude, raises the question of whether this activity has functional significance. Nonetheless, the results of some lesion studies support the notion that nonlabyrinthine inputs could be functionally important in signaling large alterations in body position in space, thereby providing for recovery of responses that were previously elicited by inputs from the inner ear.

Following a bilateral vestibular neurectomy, there is instability in blood pressure during 60° head-up rotations of the body; such movements have a tendency to generate orthostatic hypotension, which is opposed by vestibular influences on the sympathetic nervous system [12]. However, the posturally-related perturbations in blood pressure dissipated after approximately 1 week [12], as illustrated in Figure 5A. Other studies showed that vasoconstriction occurs in the lower body during 60° head-up rotations, and that this response is attenuated following a bilateral vestibular neurectomy but recovers over time [28]. In contrast, bilateral lesions of the caudal portions of the vestibular nuclei resulted in long-lasting or permanent impairments in adjusting blood pressure during postural alterations [18], as shown in Figure 5C. These findings demonstrate that integrity of the vestibular nuclei is essential for recovery of posturally-related autonomic responses following the loss of labyrinthine inputs. However, these data do not prove that modulation of vestibular nucleus neuronal activity during postural changes is required for compensation to occur after damage to the inner ear. An alternate possibility is that spontaneous firing of vestibular nucleus neurons is adequate to support the activity of cells in other regions that adjust blood pressure during movement in accordance with signals they receive from nonlabyrinthine receptors.

Recovery of posturally-related cardiovascular responses following a bilateral vestibular neurectomy also requires that the caudal cerebellar vermis, particularly the uvula (lobule IX), remain intact [10]. Stimulation of the cerebellar uvula produces profound changes in blood pressure [1,2], and the brainstem regions receiving inputs from the uvula include the caudal portions of the vestibular nuclei [19] that mediate vestibular-autonomic responses [31]. These observations indicate that the cerebellar uvula could modulate vestibular influences on cardiovascular regulation. Ablation of the uvula had little effect on posturally-related cardiovascular adjustments, although the combination of a uvulectomy and a bilateral vestibular neurectomy produced serious consequences on cardiovascular regulation. Following this combination of lesions, large decreases in blood pressure occurred when the animals were tilted head-up at amplitudes of 60°, and the deficiency in adjusting blood pressure did not dissipate over time [10], as shown in the Figure 5B. As such, both bilateral lesions of the vestibular nuclei and a bilateral vestibular neurectomy combined with a uvulectomy had similar effects on cardiovascular regulation. Additional experiments are required to decipher the physiological role of the posterior cerebellar vermis in cardiovascular regulation, particularly after the loss of labyrinthine inputs.

The functional significance of nonlabyrinthine inputs to the vestibular nuclei

Despite the prevalence of inputs from the skin, muscles, and viscera to the vestibular nuclei [13], it is currently unclear how this sensory information affects the processing of signals from the labyrinth. It seems likely that nonlabyrinthine inputs provide additional data to the central vestibular system that could be employed to decipher body position in space, but how the signals are utilized is not known. The notion that nonlabyrinthine inputs play an important role in recovery of postural responses after damage to the inner ear is well-established [5,6,25], and substitution of somatosensory and visual cues for lost labyrinthine input is a key concept employed by physical therapists during vestibular rehabilitation [3,8,9]. Nonetheless, it remains undetermined whether compensation following peripheral vestibular damage involves the enhancement of nonlabyrinthine inputs to the central vestibular system, or is dependent on

neural pathways separate from those that mediate vestibular reflexes. Further research is needed to answer this important question.

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Chronic Labyrinthectomy

Labyrinth Intact

Fig. 1.

Matrix showing the convergence of limb inputs onto vestibular nucleus neurons. The shading of each pair of boxes indicates whether a unit responded to stimulation of forelimb (F) or hindlimb (H) nerves containing muscle afferents. Different shading patterns designate whether the unit's firing was affected by low current intensities that only activated large afferents from muscle spindles and Golgi tendon organs or higher intensities that also stimulated small afferents. The top panel shows findings from animals that had previously sustained a bilateral vestibular neurectomy, whereas the bottom panel provides information from labyrinth-intact animals. Data are from [13].

Fig. 2.

The rate and coefficient of variation (CV) of spontaneous activity of vestibular nucleus neurons before and in the first week following removal of vestibular inputs through a bilateral vestibular neurectomy. Data were collected from two animals that were conscious during recordings, as described in [16].

Fig. 3.

Characteristics of vestibular nucleus neuronal responses to vertical rotations following the removal of labyrinthine inputs. Data were collected either from conscious animals or decerebrate cats that sustained a bilateral vestibular neurectomy approximately two months before the acute recording session. **A:** Bode plots indicating the response dynamics of neurons in animals lacking labyrinthine inputs. Response gain and phase are plotted with respect to stimulus position. **B:** Polar plot showing the response vector orientations of vestibular nucleus neurons following a bilateral vestibular neurectomy. Numbers along the radius of the plot indicate gain (spikes/s/°). Abbreviations: CED, contralateral ear down roll; IED, ipsilateral ear down roll; ND, nose down pitch; NU, nose up pitch. Data are from [16,32].

Fig. 4.

Responses to rotations in vertical planes of a neuron in the caudal fastigial nucleus of a conscious cat that had sustained a bilateral vestibular neurectomy. **A:** Examples of responses to sinusoidal pitch tilts at three different frequencies; the response vector orientation of the neuron was only 6° from the pitch plane, and its activity increased during head-up tilts. The amplitudes of rotations were 15° at 0.05 and 0.1 Hz and 10° at 0.5 Hz. The number of sweeps averaged to generate each trace are as follow: 0.05 and 0.1 Hz, 10; 0.5 Hz, 50. **B:** Bode plot indicating the response dynamics of the neuron; response gain and phase are plotted relative to stimulus position.

Fig. 5.

Changes in arterial blood pressure recorded in conscious cats during 60° head-up tilts subsequent to peripheral or central vestibular system lesions. Each panel shows averaged data from a single animal. To simplify comparisons, the blood pressure changes were plotted relative to those that occurred before lesions. Responses recorded in the first week following lesions are depicted by dashed lines, and those determined during the subsequent three weeks are indicated by solid lines. Error bars represent one standard error. **A:** responses recorded following a bilateral vestibular neurectomy; data are from [12]. **B:** responses recorded following a combined ablation of the cerebellar uvula and a bilateral vestibular neurectomy; data are from [10]. **C:** responses recorded following placing chemical lesions bilaterally in the caudal vestibular nuclei; data are from [18].