Adaptation of Orientation Vectors of Otolith-Related Central Vestibular Neurons to Gravity

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Eron JN, Cohen B, Raphan T, Yakushin SB. Adaptation of orientation vectors of otolith-related central vestibular neurons to gravity. J Neurophysiol 100: 1686–1690, 2008. First published May 21, 2008; doi:10.1152/jn.90289.2008. Behavioral experiments indicate that central pathways that process otolith-ocular and perceptual information have adaptive capabilities. Because polarization vectors of otolith afferents are directly related to the electro-mechanical properties of the hair cell bundle, it is unlikely that they change their direction of excitation. This indicates that the adaptation must take place in central pathways. Here we demonstrate for the first time that otolith polarization vectors of canal-otolith convergent neurons in the vestibular nuclei have adaptive capability. A total of 10 vestibular-only and vestibular-plus-saccade neurons were recorded extracellularly in two monkeys before and after they were in side-down positions for 2 h. The spatial characteristics of the otolith input were determined from the response vector orientation (RVO), which is the projection of the otolith polarization vector, onto the head horizontal plane. The RVOs had no specific orientation before animals were in side-down positions but moved toward the gravitational axis after the animals were tilted for extended periods. Vector reorientations varied from 0 to 109° and were linearly related to the original deviation of the RVOs from gravity in the position of adaptation. Such reorientation of central polarization vectors could provide the basis for changes in perception and eye movements related to prolonged head tilts relative to gravity or in microgravity.

INTRODUCTION

Activity of the hair cells embedded in the maculae of the utricles and saccules can be represented by a polarization vector, which codes their orientation relative to gravity (Fernandez and Goldberg 1976; Fernandez et al. 1972). Excitation of otolith afferents is maximal when the head is positioned so that the polarization vectors of these cells are aligned with the axis of gravity or the equivalent acceleration of gravity (a<sub>g</sub>). The maximal sensitivity of the otolith hair cells is morphologically predetermined by mechano-electrical transduction (Hudspeth and Corey 1977), and in extended experiments, otolith afferents did not adapt their polarization vectors (Fernandez and Goldberg 1976). Yet there are behaviors that adapt to prolonged orientation of the head relative to gravity or to being in microgravity during space flight. The most likely locus for this orientation adaptation is in central otolith pathways.

Perceptual estimates of the spatial vertical are altered if the head is in side-down positions for several hours (Correia 2001). Additionally, ocular counter-rolling (OCR), which torts the eyes to maintain the orientation of the retina relative to the spatial vertical, was substantially reduced in monkeys and in some humans for prolonged periods following after spaceflight (Dai et al. 1994; Yakovleva et al. 1982). Smaller changes in OCR have been reported if the head is held side down for much shorter periods (Pansell et al. 2005). OCR also equilibrates rapidly after unilateral labyrinthine lesions (Kim et al. 2008). Thus although there is evidence that otolith polarization vectors are adapted in central vestibular neurons, it has never been demonstrated experimentally.

Probable candidates for adaptation in central otolith pathways are cells that receive multiple convergent otolith inputs. These include “pure” otolith neurons as well as otolith-canal convergent neurons (Baker et al. 1984; Curthoys and Markham 1971; Dickman and Angelaki 2002; Duensing and Schaefer 1959) that can be involved in spatial orientation of the angular vestibuloocular reflex (aVOR) (Yakushin et al. 2003). Here we present findings that demonstrate that there are changes in the orientation of otolith vectors of vestibular-only (VO) and vestibular-plus-saccade (VPS) neurons with canal-otolith convergent inputs that could underlie the adaptive changes in orienting behaviors. Preliminary data have been presented (Eron et al. 2006).

METHODS

Eight VO and two VPS neurons that received convergent input from the semicircular canals and the otolith organs form the basis for this study (Table 1). The neurons were recorded extracellularly in the rostral medial and superior vestibular nuclei of two cynomolgus monkeys (Macaca fascicularis). The experiments were approved by the Institutional Animal Care and Use Committee and conformed to the Guide for the Care and Use of Laboratory Animals.

A head mount implanted on the skull provided head fixation in stereotaxic coordinates (Sirota et al. 1988; Yakushin et al. 2000). During experiments, animals sat in a primate chair in a multi-axis rotator. Neurons that received input from body proprioceptors, identified by pressing on the neck and body, were excluded from analysis, as were cells related to eye position and/or eye velocity. Two criteria were used to verify that the same neuron was recorded throughout the experiment: convergent input(s) for each neuron from the individual semicircular canals must have been the same throughout the experiment and the shape of the action potentials should not have changed substantially over the course of the experiment (Eron et al. 2007).

The convergent semicircular canal-related inputs were initially studied before and after adaptation in a side down position by
sinusoidally oscillating animals at 0.2 Hz about a spatial vertical axis with the head at different angles in pitch. This determined whether there was lateral and/or vertical canal input. If peak activation occurred with the head tilted back ~50°, there was vertical canal input. If peak activation occurred with the head tilted forward ~30°, the unit had lateral canal input (Yakushin et al. 1998). The specific vertical canal input was further characterized as described in a previous publication (Yakushin et al. 2006).

Determining the spatial sensitivity of neurons to static otolith input

The sensitivity of a neuron to gravity in three dimensions can be characterized by its polarization vector. It was not possible, however, to determine the polarization vector in this study because it would require that animals be upside down, which would make the recordings unstable. Instead we used the RVO, which is a projection of the polarization vector onto the horizontal plane in head coordinates because it only requires tilting animals over small angles from the upright (Schor et al. 1984).

To determine the RVO, the animal was tilted 30° about a spatial horizontal axis from the upright. Before each tilt, the head was reoriented in yaw in 15° increments over 180° (Fig. 1A). Because the otolith organs respond to acceleration, the equivalent acceleration of gravity, $a_g$, was considered to be the activating stimulus. Thus when the head was tilted nose-down, $a_g$ was along the mid-sagittal plane at 180° in head coordinates (Fig. 1A, left inset). Side-down head tilts to the left (LSD) or nose-up tilts corresponded

![Image of Table 1](image-url)

TABLE 1. Changes of the otolith sensitivity and response vector orientation of central vestibular neurons

<table>
<thead>
<tr>
<th>Unit</th>
<th>Type of Neuron</th>
<th>Convergent Canal Input</th>
<th>Otolith Sensitivity Before Orientation Adaptation</th>
<th>Otolith Sensitivity After Orientation Adaptation</th>
<th>RVO Before Orientation Adaptation, °</th>
<th>RVO After Orientation Adaptation, °</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VO</td>
<td>cLC</td>
<td>2.1 ± 0.3</td>
<td>4.4 ± 0.4</td>
<td>45 ± 7</td>
<td>296 ± 4</td>
</tr>
<tr>
<td>2</td>
<td>VO</td>
<td>PC</td>
<td>17.0 ± 1.3</td>
<td>7.7 ± 1.4</td>
<td>292 ± 4</td>
<td>271 ± 10</td>
</tr>
<tr>
<td>3</td>
<td>VO</td>
<td>cLC, AC</td>
<td>19.3 ± 2.1</td>
<td>16.5 ± 2.1</td>
<td>120 ± 6</td>
<td>88 ± 7</td>
</tr>
<tr>
<td>4</td>
<td>VO</td>
<td>AC</td>
<td>12.4 ± 0.9</td>
<td>9.9 ± 0.8</td>
<td>180 ± 5</td>
<td>179 ± 5</td>
</tr>
<tr>
<td>5</td>
<td>VO</td>
<td>PC</td>
<td>5.9 ± 0.5</td>
<td>5.5 ± 0.3</td>
<td>335 ± 5</td>
<td>338 ± 3</td>
</tr>
<tr>
<td>6</td>
<td>VO</td>
<td>cLC, AC</td>
<td>15.1 ± 0.5</td>
<td>11.6 ± 0.8</td>
<td>58 ± 2</td>
<td>347 ± 4</td>
</tr>
<tr>
<td>7</td>
<td>VO</td>
<td>AC</td>
<td>7.5 ± 0.6</td>
<td>8.1 ± 0.6</td>
<td>243 ± 4</td>
<td>270 ± 4</td>
</tr>
<tr>
<td>8</td>
<td>VPS</td>
<td>PC</td>
<td>7.7 ± 0.6</td>
<td>8.5 ± 0.5</td>
<td>294 ± 4</td>
<td>257 ± 3</td>
</tr>
<tr>
<td>9</td>
<td>VPS</td>
<td>cLC, PC</td>
<td>18.7 ± 1.6</td>
<td>16.0 ± 1.2</td>
<td>303 ± 5</td>
<td>270 ± 4</td>
</tr>
<tr>
<td>10</td>
<td>VO</td>
<td>cLC</td>
<td>5.5 ± 0.7</td>
<td>8.0 ± 0.5</td>
<td>76 ± 7</td>
<td>85 ± 3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>11.12 ± 0.91</td>
<td>9.62 ± 0.86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. Convergent semicircular canal input: anterior canal (AC), posterior canal (PC), and lateral canal (LC); i, ipsilateral; c, contralateral; RVO, response vector orientation; VO, vestibular only; VPS, vestibular plus succade.
to $\alpha$ at 270° and 360° in head coordinates, respectively (Fig. 1A, insets).

Each tilt activated the semicircular canals and dynamic otolith afferents (Angelaki et al. 2002) as well as static otolith afferents. These tilts produced initial increases in firing rate that declined with a time constant of <20 s (Fig. 1C). Therefore animals were held in tilted positions for ≥40 s, and the mean firing rates over the last 20 s were taken as steady-state firing rate. Steady-state firing rates were plotted as a function of the directions of $\alpha$, in the horizontal plane of the head. The average value of the function was subtracted from the data, and the sensitivity was computed by dividing the residual by $g$.

The sensitivity values (imp/s−1/g) were fit with a sinusoidal function, $y = S_{max}\cos(x + b)$. The angle $b$ was the orientation of $\alpha$ in head coordinates where there was maximal sensitivity ($S_{max}$; Fig. 1D). This angle is the RVO (Fig. 1E). The significance of the sinusoidal fit through the data ($P < 0.05$) was estimated by using Spearman’s correlation coefficient for nonlinear regression (Glantz and Slinker 1990). The average $S_{max}$ for neurons in this study was 11.1 ± 0.91 imp/s−1/g at the beginning and 9.6 ± 0.86 imp/s−1/g at the end of experiment (Table 1). Differences between the two curves were determined based on a $F$-statistic (Fig. 2, B and C), which is a reduced case of ANOVA (Glantz and Slinker 1990; Yakushin et al. 1995).

Initially, we were studying aVOR gain changes with the animals in side-down positions for 2 h (Yakushin et al. 2003), when it became obvious that the RVOs of the units were adapting their orientations toward $\alpha$. Five units (units 1–5; group 1; Fig. 2B) were recorded in the first series of experiments. In succeeding experiments, the animals were simply held in the side-down position for 2 h, and five additional units were recorded (units 6–10; group 2; Fig. 2C). There was no difference in the vector reorientation in the two groups, and they were combined. To simplify comparison, the data are presented as if the head was always positioned LSD.

RESULTS

Before being side down, the RVO of a typical unit in group 1 was 45°. After adaptation, the RVO was 296° or (−64°) (Fig. 2A, B, and I). Thus the RVO had shifted 109° in the horizontal plane of the head toward the spatial vertical [45° − (−64°)]. Two other neurons with convergent canal input also adapted their orientation vectors during tilts while undergoing aVOR adaptation (Fig. 2B, 2 and 3). This included both upward (2) and downward (3) deviations of the RVOs, one along $\alpha$ and the second along g. Two neurons that had their RVOs along the naso-occipital axis did not shift their orientation (Fig. 2B, 4 and 5).

All five of the additional units that were recorded with animals simply held in a side-down position for 2 h (group 2; Fig. 2C) had changes in RVOs toward the spatial vertical (Fig. 2B). Unit 6 adapted its orientation from one side of the mid-sagittal plane to the other as did unit 1. Units 7–9 tended to align their RVOs with the spatial vertical, similar to unit 2. One unit (10) that had its RVO close to the spatial vertical only had a small change in orientation when the animal was put on its side (Fig. 2C, 10). The average changes in RVO for the two groups were approximately equal (33 and 35°). Therefore we concluded that head orientation in the side-down position was the common factor that had caused adaptation of the otolith orientation vector (RVO). In the overall group, the shifts in RVO were significant at $P < 0.05$ (1, 2, and 6–9) or close to it (3; Fig. 2, B and C). The changes in RVO were not significant in one unit (10), but its initial RVO was close to $\alpha$. Units 4 and 5 had significance levels ($P > 0.05$), but their RVOs were approximately orthogonal to the plane of the head tilt with the animals upright or on-side (Fig. 2, B and C).

A striking finding was that there was a proportional relationship in the combined data for 6 of the 10 neurons in which the changes in the RVO were on the same side of the mid-sagittal plane (Pearson’s correlation coefficient, $r = 0.835$, $P = 0.0388$; Fig. 2D). Two other neurons had large shifts in their RVOs toward $\alpha$ (Fig. 2, B, I, 109°; and C, 6, 71°), but the magnitude of the shifts did not fall within ±1 SD of the...
relationship for the other six neurons. This may have been related to the original orientations of the RVOs of these neurons, which changed across the mid-sagittal plane. Regardless, simple side-down positioning was adequate to induce changes in RVOs of 8 of the 10 neurons toward the gravitational axis.

**DISCUSSION**

The data show that the otolith vectors of VO and VPS neurons tend to align with the gravitational axis when animals are held in side-down positions for extended periods. This study required holding single neurons for ~8 h while animals were tilted and rotated to determine the convergent semicircular canal inputs and otolith orientation vectors. Despite this technical challenge, it was possible to demonstrate that the RVOs shifted toward the upward acceleration of gravity, \( a_g \), in 7 of the 10 neurons from two animals. In one other cell (3), the vector shifted toward the downward gravitational force, \( g \). This implies that orientation shifts toward the gravitational axis are a common characteristic of VO and VPS neurons.

In six of these neurons, there was a tight linear relationship across the two animals between the angular change in the RVO relative to gravity when the head was in a tilted position. In two other cells whose angular shifts crossed the mid-sagittal plane, there were also large changes in the RVOs toward \( a_g \). We infer that the angular disparity between the RVO and the gravitational axis was driving the adaptation process. Units 4 and 5 did not change their vector orientation. Their RVO’s were orthogonal to gravity both in the upright and side-down positions, and this may have been responsible for the lack of adaptation. If the orthogonality of the RVO relative to gravity in upright and side-down positions is important, then the RVO’s of units 4 and 5 should change if the animals had been adapted in prone or supine.

How is the reorientation toward the gravitational axis generated? Central vestibular neurons receive multiple afferent inputs from various parts of the otolith organs, and there are both ipsi- and contralateral projections from the otolith organs to central vestibular neurons (Uchino 2001; Uchino et al. 1997; Wilson et al. 1978). If the weights of the convergent inputs were differentially adapted when the head was held for prolonged periods relative to gravity, it would change the orientation of the combined otolith vectors. These weight changes could also be responsible for the observed sensitivity changes if the vector normalization was not maintained in the horizontal plane. Such weight alterations would also explain why there is no adaptation toward the spatial vertical when upright. If the convergent otolith afferents were close to the plane of the utricle, for example, no alteration in weighting could orient a central recipient cell toward the vertical while the animal was upright. If the animal was side-down, however, the cell could change its vector orientation, so that its polarization would point along the interaural axis, closer to alignment with gravity. Similarly, the saccules could provide input for cells with vectors pointed either toward or away from gravity (Uchino et al. 1997) or when animals were upright, but not when they were on-side.

Based on this hypothesis, cells that received input predominantly from the sacculus would rotate their otolith vector close to the approximate sagittal plane of the head in prone or supine positions. Such differences in convergent inputs could determine the amount of plasticity in different head positions, as in units 1 and 6, versus the smaller changes in the other units. Thus changes in orientation are likely to be constrained by the orientation of individual polarization vectors of primary otolith afferents that converge onto central vestibular neurons.

If the observed changes in orientation of the RVO recorded in VO and VPS neurons are related to the estimation of the spatial vertical relative to the head vertical, then the adaptation of these neurons could be coding the orientation changes. VO and VPS neurons project to the flocculus (Zhang et al. 1993, 1995), which could be the neural path for implementing these adaptive changes.

Two types of adaptation have been described in behavioral studies that could be related to the changes in orientation of the units considered in this study. In one, the gain of OCR was decreased when monkeys (Dai et al. 1994) or humans (Yakovleva et al. 1982) returned from spaceflight. It has been postulated that this occurs because of the lack of an otolith input during head tilt or head roll in microgravity, which only excites the semicircular canal and neck afferents, not the otolith organs (Young et al. 1984). Another type of adaptation involves a change in the perception of tilt induced by centrifugation during and after exposure to microgravity (Clement et al. 2001). Initially, on insertion into microgravity 1 g of centripetal acceleration in microgravity was perceived as a 45° tilt, as on Earth, despite the absence of gravity. Only after 2 wk in space did the same centrifugation induce a perception of tilt of 90°, aligned with the centripetal linear acceleration.

It has been posited that both the gain of OCR and the perception of the spatial vertical are related to a cross product between the net linear acceleration on the body, i.e., the “perceived spatial vertical” and the “idiotropic vertical” (Mittelstaedt 1992), which lies along the \( z \) axis of the head (Clement et al. 2001; Maruta et al. 2007; Raphan and Cohen 2002; Raphan et al. 1996). Because the magnitude of a cross-product depends on the angle between the vectors, a closer alignment of the idiotropic vector and the estimate of the spatial vertical would reduce the magnitude of the cross-product and the drive for generating OCR, as well as the perception of the vertical. Thus the spatial orientation shifts in these neurons could provide the cellular basis for these changes.

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