Inactivation of Semicircular Canals Causes Adaptive Increases in Otolith-Driven Tilt Responses

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1Department of Neurobiology, Washington University School of Medicine, St. Louis, Missouri 63110; 2Department of Otolaryngology, University of Texas Medical Branch, Galveston, Texas 77550; and 3Department of Research, Central Institute for the Deaf, St. Louis, Missouri 63110

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Angelaki, Dora E., Shawn D. Newlands, and J. David Dickman. Inactivation of semicircular canals causes adaptive increases in otolith-driven tilt responses. J Neurophysiol 87: 1635–1640, 2002; 10.1152/jn.00775.2001. Growing experimental and theoretical evidence suggests a functional synergy in the processing of otolith and semicircular canal signals for the generation of the vestibulo-ocular reflexes (VORs). In this study we have further tested this functional interaction by quantifying the adaptive changes in the otolith-ocular system during both rotational and translational movements after surgical inactivation of the semicircular canals. For 0.1–0.5 Hz (stimuli for which there is no recovery of responses from the plugged canals), pitch and roll VOR gains recovered during earth-horizontal (but not earth-vertical) axis rotations. Corresponding changes were also observed in eye movements elicited by translational motion (0.1–5 Hz). Specifically, torsional eye movements increased during lateral motion, whereas vertical eye movements increased during fore-aft motion. The findings indicate that otolith signals can be adapted according to a compromised strategy that leads to improved gaze stabilization during motion. Because canal-plugged animals permanently lose the ability to discriminate gravitoinertial accelerations, adapted animals can use the presence of gravity through otolith-driven tilt responses to assist gaze stabilization during earth-horizontal axis rotations.

INTRODUCTION

All naturally occurring pitch and roll head tilts occur about earth-horizontal axes that are associated with a dynamic activation of both semicircular canal and otolith vestibular sensors. Despite the presence of separate organs for detecting angular and linear accelerations, the vestibulo-ocular reflexes (VORs) should be functionally organized in a comprehensive, synergistic manner whereby both input signals are centrally processed together according to the specific functional demands for gaze stabilization. Even though under normal conditions this synergistic interaction often remains unnoticed, altered functional demands placed on the system after selective lesions or exposure to altered visual or gravitational environments could potentially reveal this underlying organization. The need for such a functional synergy and multisensory processing has been proposed in several experimental and modeling studies of the vestibular system (Angelaki et al. 1999; Guedry 1974; Merfeld 1995; Merfeld et al. 1999; Young 1974; Zupan et al. 2000).

Since most naturally occurring tilting (i.e., rotational) movements are accompanied by a concurrent change of the head relative to gravity, primary otolith afferents respond to both translational and tilting movements (e.g., Anderson et al. 1978; Angelaki and Dickman 2000; Fernandez and Goldberg 1976; Loe et al. 1973). Nevertheless, VOR responses are similar during earth-vertical and earth-horizontal axis rotations, suggesting that gravity-related otolith signals do not contribute to the primate angular VOR (AVOR) above approximately 0.05–0.1 Hz (Angelaki and Hess 1996b; Merfeld and Young 1995; Tweed et al. 1994). Thus it appears as if otolith-ocular signals are selectively processed to ignore gravity and only compensate for the translational component of the movement.

Inactivation of the semicircular canals by plugging the canal lumen (Ewald 1892) results in a permanently compromised AVOR at frequencies below approximately 1 Hz (Angelaki et al. 1996; Baker et al. 1982; Böhmer et al. 1985; Broussard et al. 1999; Hess et al. 2000; Lasker et al. 1999; Paige 1983; Rabbitt et al. 1999; Yakushin et al. 1995, 1998). The deficits in canal-plugged animals are not only limited to the AVOR, but the translational VOR (TVOR) as well. Specifically, recent work from our laboratory has demonstrated that canal-plugged animals can no longer separate gravity from translational accelerations (Angelaki et al. 1999). Thus canal-plugged animals elicit a TVOR in response to any gravitoinertial acceleration, including a dynamic rotational movement relative to gravity. Under the conditions of a deficient semicircular canal system, and since gravity is no longer selectively filtered from contributing to the VOR in canal-plugged animals (Angelaki et al. 1999), otolith-ocular responses could adapt and supplement the deficient canal function in the lesioned animals. In the present study, we have investigated this hypothesis by examining the AVOR and TVOR over time after semicircular canal plugging.

METHODS

All six semicircular canals were plugged (Ewald 1892) in two juvenile rhesus monkeys (animals R and B) implanted with skull bolts to restrain the head during experiments and a dual search coil for three-dimensional eye movement recordings (Angelaki 1998). Each canal to be plugged was exposed and a small hole was drilled in the bony wall of the canal. The membranous duct was then cut with the
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tip of a sharp knife. Subsequently, the hole was firmly filled with bony chips and covered with a piece of muscle fascia. All surgeries and animal handling were in accordance with National Institutes of Health and Institutional guidelines. The effectiveness of plugging was verified by the absence of any response during low-frequency earth-vertical axis rotations (<0.5 Hz) (Angelaki et al. 1996; Hess et al. 2000).

During experiments, the monkeys were seated in a primate chair with their heads restrained in a position such that the horizontal stereotaxic plane was tilted 15° nose-down. The primate chair was subsequently placed inside a motorized three-dimensional turntable that rode on top of a linear sled. The experimental protocols were as follows.

**Translational protocols**

Animals were sinusoidally oscillated in complete darkness either along their interaural axis (lateral motion) or along their naso-occipital axis (fore-aft motion) at frequencies of 0.16 and 0.2 Hz (0.1 g peak) and 0.3–5 Hz (0.4 g peak). To minimize fluctuations in vergence angle, translation started several seconds after animals were placed in darkness. Under these conditions, vergence was maintained between 0.8–2° (corresponding to distances of approximately 50–120 cm), values too low to induce large vergence-dependent changes in the TVOR (Telford et al. 1997). 4 and 5 Hz oscillations were also delivered while animals fixated a central target at different viewing distances (10, 15, 20, 30, and 40 cm).

**Rotational protocols**

In each of the pitch and roll head planes, the AVOR was tested in darkness during rotation about both an earth-vertical (EVA) and an earth-horizontal axis (EHA) using steady-state sinusoidal oscillations at 0.1, 0.2, and 0.5 Hz (±2°). Lower frequencies were not included in the analyses to avoid activation of velocity storage. These AVOR protocols were used to compare EVA with EHA responses before, acutely, and over time after canal inactivation.

For each recording session, signals were low-pass filtered (200 Hz, 6-pole Bessel) and digitized at a rate of 833.33 Hz (Cambridge Electronics Design, model 1401). Calibrated three-dimensional eye positions were expressed as rotation vectors with straight ahead as the reference position. Angular eye velocity was computed from 3D eye position and the fast phases were removed, as previously described (c.f., Angelaki 1998; Angelaki and Hess 1996a,b). Positive directions were defined according to the right-hand rule, i.e., leftward, downward, and clockwise (from the animal’s point of view) for horizontal, vertical, and torsional eye movements, respectively. Sensitivity and phase were determined by fitting a sine function (and a DC offset) to average response cycles. For rotational stimuli, AVOR gains were computed as the ratio of eye velocity to head velocity. For translational stimuli, responses were expressed as apparent “tilt” gains which were computed as eye velocity divided by (2π) tan−1 (G) with G the linear acceleration in units of g = 981 cm/s² (see also Angelaki 1998; Telford et al. 1997). Phase was expressed as the difference (in degrees) between peak eye velocity and peak head velocity. Positive directions of linear acceleration were to the right and backward for 0.5 Hz (±22°) roll oscillations and (B) 0.5 Hz, ±0.4 g lateral translation in complete darkness (0.8–2 MA of vergence). Data were collected from animal R before, acutely after, as well as 2 mo after all semicircular canals were inactivated. Dashed lines illustrate zero position (straight-ahead gaze) and zero eye velocity. The stimulus (bottom) is either head roll position (Hhead in A) or the output of a linear accelerometer mounted on the animal’s head (Hacc in B). Sections of fast eye movements have been removed from slow-phase eye velocity plots.

**Fig. 1.** Torsional, vertical, and horizontal components of eye position (Eacc, Eacc, and Eacc) and slow-phase eye velocity (Ωacc, Ωacc, Ωacc) during (A) 0.5 Hz, ±22° roll oscillations and (B) 0.5 Hz, ±0.4 g lateral translation in complete darkness (0.8–2 MA of vergence). Data were collected from animal R before, acutely after, as well as 2 mo after all semicircular canals were inactivated. Dashed lines illustrate zero position (straight-ahead gaze) and zero eye velocity. The stimulus (bottom) is either head roll position (Hhead in A) or the output of a linear accelerometer mounted on the animal’s head (Hacc in B). Sections of fast eye movements have been removed from slow-phase eye velocity plots.

**RESULTS**

**Responses during rotation**

Roll and pitch AVORs elicited during EHA rotations with the animals upright exhibited a clear and consistent recovery over time after canal plugging. An example of 0.5 Hz roll AVOR is illustrated in Fig. 1A. Acutely after plugging, torsional and vertical eye velocity responses were negligible, whereas horizontal eye velocity modulation was larger than before plugging. These horizontal eye movements reflect the fact that canal-plugged animals can no longer discriminate gravity and translational accelerations (Angelaki et al. 1999). As a result, TVORs (horizontal eye movements) are elicited during both lateral translation and roll tilt oscillations (e.g., compare Fig. 1, A and B; see also Angelaki et al. 1999).

Both roll and pitch AVOR recovered during EHA rotations [F(4,28) = 59.9, P < 0.01]. The data from both animals have been summarized in Fig. 2, A and B. Notice that in this frequency range, semicircular canal afferent recovery is negligible, as illustrated by the dotted lines that plot the respective AVOR gain during EVA rotations 3 mo after canal plugging.

**Responses during lateral and fore-aft translation**

A similar increase in torsional and vertical eye velocity was also observed over time during lateral and fore-aft translation, respectively. As previously described in labyrinthine-intact monkeys (Angelaki 1998; Paige and Tomko 1991), lateral translation elicited mainly horizontal, but negligible torsional, eye movements (Fig. 1B, left; Before data traces). Acutely after plugging, the pattern of eye velocity modulation during translation was unchanged, with only horizontal modulation being observed (Fig. 1B, middle; Acutely after data traces; see also Angelaki et al. 1999). With time, however, torsional slow-phase eye velocity increased during lateral motion, as shown in Fig. 1B, right (2 mo after data traces). Similar increases were also observed in the vertical component during fore-aft translation.

Because these torsional/vertical eye movements can be considered compensatory to an apparent head tilt, it is convenient to describe their magnitude as tilt gains (Angelaki 1998; Paige and Tomko 1991; Telford et al. 1997). The changes in torsional/vertical tilt gains for different stimulus frequencies as a function of time after canal plugging have been summarized during lateral and fore-aft motion for both animals in Fig. 3, A and B. Notice that the increase in torsional/vertical eye velocity was not only limited to low frequencies. In fact, the largest increases were observed during mid- and high-frequency motion, primarily in the range of 0.5 to 5 Hz. The increases in torsional/vertical eye velocity during translation were statistically significant [F(2,62) = 31.0, P < 0.01]. The recovery of tilt gains during translation and AVOR gains during rotation followed similar time courses, as suggested by a nearly unity slope and a significant linear correlation between respective rotational and tilt gains (y = −0.1 + 0.9x; R² = 0.80, P < 0.01).
0.01). An increase in torsional eye velocity after plugging was observed not only in darkness but also while the animals fixated near targets during lateral translation \(F(1,6) = 133.6, P < 0.01\).

**DISCUSSION**

The present results demonstrate that inactivation of semicircular canals seems to trigger adaptive changes in the otolith-ocular system, as guided by a compromised strategy and the need to improve gaze stabilization during both translational and tilt rotational movements. These results supplement recent conclusions suggesting that there is a strong and adaptable functional synergy between the central processing of otolith and semicircular canal cues (Angelaki et al. 1999, 2000b; Merfeld 1995; Merfeld et al. 1999). This functional synergy extends well beyond a linear superposition of semicircular canal and otolith signals, as has often been suggested based on two independent TVOR and AVOR processes.

**Eye movements during translation**

Translational movements elicit mainly horizontal eye movements in primates, whereas torsional and vertical eye movements elicited in darkness or with fixation at targets with negligible vertical elevation are usually small and variable (Angelaki 1998; Angelaki and McHenry 1999; Angelaki et al. 1999, 2000a; McHenry and Angelaki 2000; Merfeld et al. 1996; Paige and Tomko 1991; Schwarz and Miles 1991; Telford et al. 1997). The small amplitude of these torsional and vertical eye movement components (which are often referred to as "orienting" or tilt responses) in monkeys and humans has been in contrast to results in lateral-eyed species that have been shown to exhibit large otolith-driven torsional and vertical eye movements during lateral and fore-aft translation (Baarsma and Collewijn 1975; Dickman and Angelaki 1999; Hess and Dieringer 1991).

Several studies have also demonstrated that EVA and EHA responses are identical, suggesting that tilt responses do not contribute to the primate AVOR above approximately 0.05–0.1 Hz, nor during short-lasting, transient pitch and roll tilts (Angelaki and Hess 1996b; Merfeld and Young 1995; Tweed et al. 1994). This conclusion has been further documented in the present study. If the otolith organs played a significant role in the AVOR, then we would have expected to see this contribution just after the canals were plugged, before any plastic changes could take place. Instead, no roll or pitch AVOR was elicited acutely after plugging. This observation is in contrast to what has been reported in rabbits, where tilt otolith-ocular reflexes have been shown to significantly contribute to the AVOR during EHA rotations (Barmack 1981; Barmack and Pettorossi 1988; Van der Steen and Collewijn 1984). There could be several explanations for these species differences. First, primate AVOR gain is high, often near unity, so there would be little advantage in a gravity-specific otolith-driven
augmentation in compensatory eye velocity during mid- and high-frequency rotations. Second, it has been often argued that a large otolith-ocular orienting response, although functionally appropriate in rabbits, would provide little advantage to subjects with a well-developed saccadic system (Vilis 1993). In fact, it has been shown that it is mostly the fast (rather than slow) phases whose torsional and vertical components are modulated as a function of gravity in primates (Angelaki and Hess 1996a; Hess and Angelaki 1997a,b). Finally, it has recently been shown that rhesus monkey (and presumably also human) VOR can correctly discriminate the true translational gravity from translational accelerations (as long as the semicircular canals are intact; Angelaki et al. 1999), a property that does not seem to be true in lateral-eyed species (Baarsma and Collewijn 1975; Barmack 1981; Barmack and Petrorossi 1988; Dickman and Angelaki 1999; Hess and Dieringer 1991; Van der Steen and Collewijn 1984). Therefore it appears that, along with a quite elaborate repertoire of binocular eye movements in the TVOR and specially evolved short-latency visuomotor reflexes (for review, see Miles 1993, 1998), the primate central vestibular system has also developed the unique ability to circumvent the inherent ambiguity of the otolith system and differentiate between gravity and translational accelerations (Angelaki et al. 1999).

Semicircular canal plugging and the VORs

Contrary to expectations, inactivation of the semicircular canals results not only in a compromised AVOR but also a compromised TVOR as well. Specifically, we have recently shown that canal-plugged animals can no longer separate gravity from translational accelerations (Angelaki et al. 1999), thus eliciting a TVOR in response to any gravito-inertial acceleration including a dynamic rotational movement relative to gravity (Fig. 1A). The loss of the ability to distinguish gravity from translational accelerations does not represent an adaptation process, since it is acutely evident after the canal plugging operation and does not recover (Angelaki et al. 1999). This result has provided strong experimental support for the hypothesis that semicircular canal signals are important in separating gravitoinertial accelerations into two functionally distinct signals associated with tilts relative to gravity and translational movements (Guedry 1974; Merfeld and Young 1995; Merfeld et al. 1999; Young 1974; Zupan et al. 2000).

Gaze stabilization challenge in canal-plugged animals

It becomes apparent that the canal-plugged VORs are now faced with totally different challenges from those experienced by labyrinthine-intact animals. Not only is the AVOR compromised, but the TVOR as well. Because of this deficit, identical eye movements are elicited during both EHA rotations and during translational movements (Fig. 1A and B). Being in this compromised state, adaptive mechanisms in the VORs have a limited set of choices. Establishing appropriate TVORs is not easily achieved without extra-vestibular signals that are clearly not available under these conditions (i.e., neither efference copy nor neck proprioceptive signals could replace the semicircular canal role and provide extra-otolith cues for the separation of gravity during passive motion with the head fixed in the body). Adaptive mechanisms could, however, improve the totally compromised AVOR by changing the direction of eye movement elicited in response to specific linear accelerations. Thus canal-plugged primates can now be more similar to rabbits and other lateral eyed species and use the presence of gravity through otolith-driven responses to assist gaze stabilization during EHA rotations. The present results suggest that this is the option chosen by the compromised primate vestibulo-ocular system.

It is important to point out that the present results and the increased contribution of otolith-ocular responses to gaze stabilization during rotations only pertain to frequencies outside the velocity storage range (i.e., higher than approximately 0.05–0.1 Hz). At lower frequencies, otolith-driven velocity storage responses not only did not improve but in fact deteriorated over time after canal plugging (Angelaki et al. 2000b). This striking difference is by no means surprising, given the fact that only mid- and high-frequency VOR is important for gaze stabilization. In contrast, the function of velocity storage and its utility and functional significance in the VOR remains questionable. The results regarding the decrease in the otolith-driven velocity storage responses are in fact consistent with the idea that low-frequency otolith signals do not simply enhance VOR responses but might be involved in spatial orientation aspects that have little to do with gaze stabilization per se (Angelaki et al. 2000b).

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