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Oculomotor Plasticity During Vestibular Compensation Does Not Depend on Cerebellar LTD

M. Faulstich,[1],* A. M. van Alphen,[2],* C. Luo,[2] S. du Lac,[1,3] and C. I. De Zeeuw[2]

[1]*Systems Neurobiology Laboratory, Salk Institute, La Jolla California;* [2]*Department of Neuroscience, Erasmus MC, Rotterdam, The Netherlands; and* [3]*Howard Hughes Medical Institute*

Faulstich, M., A. M. van Alphen, C. Luo, S. du Lac, and C. I. De Zeeuw. Oculomotor plasticity during vestibular compensation does not depend on cerebellar LTD. *J Neurophysiol* 96: 1187–1195, 2006. First published May 24, 2006; doi:10.1152/jn.00045.2006. Vestibular paradigms are widely used for investigating mechanisms underlying cerebellar motor learning. These include adaptation of the vestibuloocular reflex (VOR) after visual-vestibular mismatch training and vestibular compensation after unilateral damage to the vestibular apparatus. To date, various studies have shown that VOR adaptation may be supported by long-term depression (LTD) at the parallel fiber to Purkinje cell synapse. Yet it is unknown to what extent vestibular compensation may depend on this cellular process. Here we investigated adaptive gain changes in the VOR and optokinetic reflex during vestibular compensation in transgenic mice in which LTD is specifically blocked in Purkinje cells via expression of a peptide inhibitor of protein kinase C (L7-PKCi mutants). The results demonstrate that neither the strength nor the time course of vestibular compensation are affected by the absence of LTD. In contrast, analysis of vestibular compensation in spontaneous mutants that lack a functional olivocerebellar circuit (*lurchers*) shows that this form of motor learning is severely impaired. We conclude that oculomotor plasticity during vestibular compensation depends critically on intact cerebellar circuitry but not on the occurrence of cerebellar LTD.

INTRODUCTION

The vestibuloocular reflex (VOR) provides an excellent model for understanding neural mechanisms of motor learning. The VOR stabilizes images on the retina during self-motion by producing eye movements that compensate for motion of the head. Under normal circumstances, vestibular information is supplemented by vision, such that the gain of the combined visual-VOR is near unity (i.e., perfectly compensatory). Prolonged periods of discrepant visual and vestibular information result in powerful forms of motor learning in the VOR that serve to minimize retinal image motion during head movements. Two qualitatively distinct forms of motor learning have been investigated intensively over the past several decades. The first, termed "VOR adaptation," is evoked by persistent image motion on the retina during eye or head movement. The second, termed "vestibular compensation," is evoked by unilateral loss of peripheral vestibular function. In both VOR adaptation and vestibular compensation, adaptive increases in the gain of the VOR serve to restore gaze stability during head motion. The extent to which the mechanisms of compensation and adaptation are shared remains to be determined.

The cerebellum is critical for inducing the adaptive gain changes that occur during both VOR adaptation (Ito et al. 1982; Koekkoek et al. 1997; Lisberger et al. 1984; Michnovicz and Bennett 1987; Nagao 1983; Pastor et al. 1994; Robinson 1976) and vestibular compensation (Courjon et al. 1982). Purkinje cells in the cerebellar flocculus receive synaptic inputs from granule cells that convey information about head and eye motion as well as from neurons of the inferior olive that signal retinal image motion. A particular cell physiological mechanism, long-term depression (LTD) of granule cell synapses onto Purkinje cells, has been proposed to account for the adaptive increases in VOR gain induced by the conjunction of image motion and head movement (Ito et al. 1982). Cerebellar LTD occurs in vivo when climbing fiber axons from the inferior olive are stimulated conjunctively with parallel fiber axons from granule cells (Coesmans et al. 2004). The signaling pathways and molecular mechanisms of cerebellar LTD have been studied extensively in vitro (reviewed in Ito 2001, 2002; Linden and Connor 1995), and include phosphorylation of GluR2 and delta GluR2 subunits by protein kinase C (Hirai et al. 2003; Kondo et al. 2005; Leitges et al. 2004; Linden and Connor 1991).

Accumulating evidence implicates parallel fiber LTD in behavioral plasticity mediated by the cerebellum, including adaptation of compensatory eye movements (Feil et al. 2003; Shutoh et al. 2002, 2003). To overcome the limitations of global modifications in gene expression, a line of mice deficient in cerebellar LTD was generated by expressing a peptide inhibitor of PKC specifically in Purkinje cells under the L7 promoter (De Zeeuw et al. 1998). Purkinje cells in heterozygous L7-PKCi mice have normal spontaneous and evoked firing properties but lack cerebellar LTD both in culture and in brain slices as well as in vivo (De Zeeuw et al. 1998; Gao et al. 2003; Goossens et al. 2004; Goossens et al. 2001). L7-PKCi mice exhibit aberrant classical conditioning of eye blink responses (Koekkoek et al. 2003) and are impaired in the ability to generate adaptive gain changes in the VOR after visual-vestibular mismatch training (De Zeeuw et al. 1998). These findings suggest a critical role for LTD in cerebellar learning in general and adaptive gain changes in the VOR in particular.

A number of observations in L7-PKCi mice, however, indicate that cerebellar LTD cannot account for all forms of adaptive plasticity in the oculomotor system. The dynamics of both the VOR and the optokinetic reflex (OKR) are normal in mice lacking LTD (De Zeeuw et al. 1998), implying that

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developmental calibration of cerebellar-dependent eye movements proceeds independently of LTD. Moreover, when prolonged periods of visual-vestibular training are provided, L7-PKCi mice can ultimately obtain the same VOR gain and phase values as wild-type mice, although at a slower pace (van Alphen and De Zeeuw 2002). Thus adaptive gain changes in the VOR are able to utilize mechanisms that are distinct from LTD.

The current study investigates whether cerebellar LTD is required for oculomotor plasticity induced during vestibular compensation. The effects of unilateral damage to the vestibular periphery on the VOR and OKR were examined in both heterozygote and homozygote lines of L7-PKCi mice as well as in wild-type mice. Moreover, to find out to what extent the olivo-cerebellar circuit as a whole may contribute, vestibular compensation was analyzed in *Lurcher* mice, which are known to lack Purkinje cells and to have reduced numbers of granule cells and inferior olive neurons (Caddy and Biscoe 1979).

Although oculomotor performance was impaired in L7-PKCi homozygote compared with that in heterozygotes and wild-type mice, adaptive gain increases in the VOR and OKR were equally robust in both strains of L7-PKCi mice and in wild-type mice. In contrast, *Lurcher* mice were completely impaired in their ability to increase oculomotor gain after vestibular damage. These results demonstrate that vestibular compensation requires functional cerebellar circuitry but does not depend on cerebellar LTD.

METHODS

Search coil and headpost surgeries

Mice were anesthetized with a mixture of halothane, nitrous oxide, and oxygen. An acrylic head fixation pedestal was formed and fixed to the skull by five screws (M1, 1.5 mm). Screws were implanted on the frontal, parietal, and interparietal bone plates. After completion of the construct, the head was positioned in a 70° roll so the eye could be easily approached. A small incision was made in the conjunctiva on the temporal side of the eyeball. A pocket was bluntly dissected anterior to the insertion of the lateral rectus muscle. A copper wire coil (1 mm OD, 60 turns, 1.0 mg) was placed in the pocket. The coil was fixed to the sclera with two sutures (10/0 nylon, Ethicone). The sutures were approximately aligned in the equatorial plane of the eye. The conjunctiva was closed over the coil with an additional suture. The leads of the coil were carefully tunneled underneath the conjunctiva and the skin to a miniature coaxial MMCX connector that was attached to the top of the acrylic head pedestal. All animals were allowed to recover for ≥3 days before the first eye-movement recordings were made.

Vestibular damage

Under deep halothane anesthesia, a small postauricular incision was made and the tissue overlying the horizontal semicircular canal was dissected. The horizontal semicircular canal was drilled open over a length of ~1 mm, and endolymphatic fluid was drained until spontaneous flow ceased. Using a blunt 30-gauge needle attached to a 2-ml syringe, air was flushed through the opened canal to expel remaining endolymphatic fluid and mechanically disrupt the sensory epithelia. A small dental paper tip (size 15) was introduced into the rostral canal opening and fixed in place with bone wax, which was also used to seal up the caudal canal opening. The wound was closed and sutured with two or three stitches of 6/0 suture, and the animal was restrained in the animal holder where it was allowed to wake up.

Measurement of eye movements

On recording, mice were immobilized in a custom-made restrainer incorporating an aluminum plate to which the mouse's head fixation pedestal was bolted. The restraint assembly was mounted within magnetic field coils (CNC Engineering, Seattle, WA) atop a vertical-axis turntable (Biomedical Engineering, Thornwood, NY). The midpoint of the interaural line was placed in the center of rotation for the optokinetic drum and the turntable. The field coils were attached to the turntable and moved with the animal. Optokinetic stimuli were delivered with a striped drum (width of bars was 4°). The drum had a diameter of 26 cm and enclosed the animal. The VOR was evaluated during sinusoidal, whole body rotation in the dark. Eye position and stimulus recordings were filtered on-line at 20 Hz using a fourth-order Bessel filter (Axon Instruments) and digitized at 250 Hz with 32-bit precision (CED, Cambridge, UK). Before each recording session, the eye coil was calibrated by rotating the field coils around the animal. During rotation of the field coils the animal was presented with an earth fixed optokinetic stimulus. The field coils were rotated around the animal over an angle of 20° and the resulting voltage was taken as a reference for the following recording session.

The OKR and VOR were measured in nine heterozygous and nine homozygous L7-PKCi transgenic mice, 14 wild-type (C57/bl6) mice and 9 *Lurcher* mice. To quantify oculomotor performance, the optokinetic reflex in response to sinusoidal movement of the drum was tested at 6 different frequencies: 0.1, 0.2, 0.4, 0.6, 0.8, and 1 Hz. Amplitude of the drum was constant at 5° (0-peak). In this manner, peak velocities ranging from 3 to 31°/s were tested. VOR in response to sinusoidal whole body rotation was tested at 5° amplitude (0-peak) in the same frequency range as the OKR. The interaction of OKR and VOR to produce a visually enhanced VOR (VORl) was elicited by whole body rotation in the light. During VORl stimulation, the animal was presented with an earth fixed drum for a stationary visual stimulus. The order in which stimuli were delivered was randomized and a recording session lasted ~30 min. The first recording after vestibular lesion was obtained 1 h after surgery and in some animals repeated recordings were made at 2, 4, and 6 h after surgery. All animals were again recorded 8 h after surgery. To exclude possible artifacts of the surgery and anesthesia on oculomotor performance, the 8-h recording was the first data point included in the analysis.

Data analysis

The following exclusion criteria were applied to eliminate data from animals for which oculomotor performance may have been influenced by factors other than the labyrinthectomy. Under the assumption that a complete labyrinthectomy would remove half of the vestibular inputs, two wild-type mice were excluded in which the postoperation VORd gain did not drop <50% of control values; these were among the first group of animals in which unilateral vestibular damage (UVD) was performed. In six animals (4 wild-type, 2 PKCi heterozygotes), an infection developed after surgical UVD that resulted in a marked and persistent decrease in gains under all stimulus conditions; these animals were excluded from the analyses of oculomotor performance following UVD.

Eye, head, and drum position were differentiated off-line, using a three-point software algorithm. Fast phases were identified based on a velocity criterion, which was set at 2.5 times the peak stimulus velocity. Identified fast phases were excised from the eye velocity trace with a margin of 20 ms before to 80 ms after detection. All cycles in a trace were taken together to construct an average eye-velocity curve. Gain of the eye movement and phase of eye movement with respect to stimulus movement were calculated by fitting a sine wave to the average response using least-square optimization under the assumption that the fundamental frequency of the eye movement equaled that of the stimulus. The degree of asymmetry between ipsiversive and contraversively directed eye movements was calcu-

lated from the offset of the sine fit. Negative phase value indicate that eye motion lagged stimulus motion. Phase relations of VOR and VORl were shifted by 180° making the phase angle zero for perfectly compensatory responses.

The extent of nystagmus caused by unilateral vestibular damage was analyzed by counting the number of fast phases that occurred when the animal was at rest in the dark. For a period of 3-min spontaneous eye movements were recorded in the dark. Fast phases were detected when eye velocity exceeded 150°/s.

Statistical differences of gain and phase between groups were tested by paired t-test while the effect of vestibular damage and recovery on gain and phase of VORl, OKR, and VORd within groups was tested by repeated-measures ANOVA. Statistical analysis was performed using commercially available software (Statview, SAS, Cary, NC).

RESULTS

Control VOR and OKR values in wild-type, PKCi mutants, and Lurcher mice

Eye movements evoked by visual and vestibular stimuli were measured with miniature scleral search coils in wild-type mice (C57/bl6), *Lurcher* mice, and transgenic mice expressing a peptide inhibitor of protein kinase C in Purkinje cells (L7-PKCi homozygotes and L7-PKCi heterozygotes). Responses to three different conditions of sensory stimulation were obtained. In the first, which assessed the VORl, mice were rotated on a turntable while viewing a stationary surround. In the second condition, the VOR was assessed by rotating mice on the turntable in complete darkness (VORd). To measure the OKR, mice viewed a drum rotating around a stationary platform. Rotational amplitude was fixed at 5° (10° peak to peak), while stimulus frequency varied from 0.1 to 1 Hz (i.e., peak stimulus velocity varied from 3 to 31°/s).

Plots of the gain (eye speed/stimulus speed) and phase (with respect to perfect compensation) of the resulting eye movements are shown in Fig. 1. In wild-type mice, the performance of the VORl was nearly constant across stimulus conditions with gains averaging 0.71 ± 0.01 (Fig. 1A) and response phases ranging from 3 to $-0.2°$ (Fig. 1D). The performance of the VORd and OKR varied across stimulus conditions in a complementary fashion as reported previously in wild-type mice (Faulstich et al. 2004; Koekkoek et al. 1997; van Alphen et al. 2001), such that VORd gains increased (from 0.08 ± 0.04 to 0.45 ± 0.09; Fig. 1B) and OKR gains decreased (from 0.69 to 0.18 ± 0.06; Fig. 1C) as stimulus frequency increased from 0.2 to 1 Hz.

Although oculomotor performance was unimpaired in L7-PKCi heterozygotes as reported previously (De Zeeuw et al. 1998), L7-PKCi homozygotes exhibited relatively low gain values (Fig. 1). VORl gains in L7-PKCi-homozygote mice increased from 0.48 ± 0.13 to 0.54 ± 0.14, and VORd gains increased from 0.06 ± 0.03 to 0.35 ± 0.11, as stimulus frequency increased from 0.2 to 1 Hz. All of these gain values were significantly lower than those in wild-types (for VORl and VORd, $P < 0.005$ and $P < 0.05$, respectively) and heterozygous L7-PKCi mice (for VORl and VORd, $P < 0.1$) except at 0.2 Hz during VORd ($P > 0.05$). Response phases were similar for the VORd in L7-PKCi homozygotes, L7-PKCi heterozygotes, and wild-types (Fig. 1E) but were advanced by ~5° during the VORl in L7-PKCi homozygotes ($P < 0.05$; Fig. 1D). OKR gains were reduced at low stimulus frequencies (0.2–0.4 Hz) in L7-PKCi-homozygotes relative to wild-type
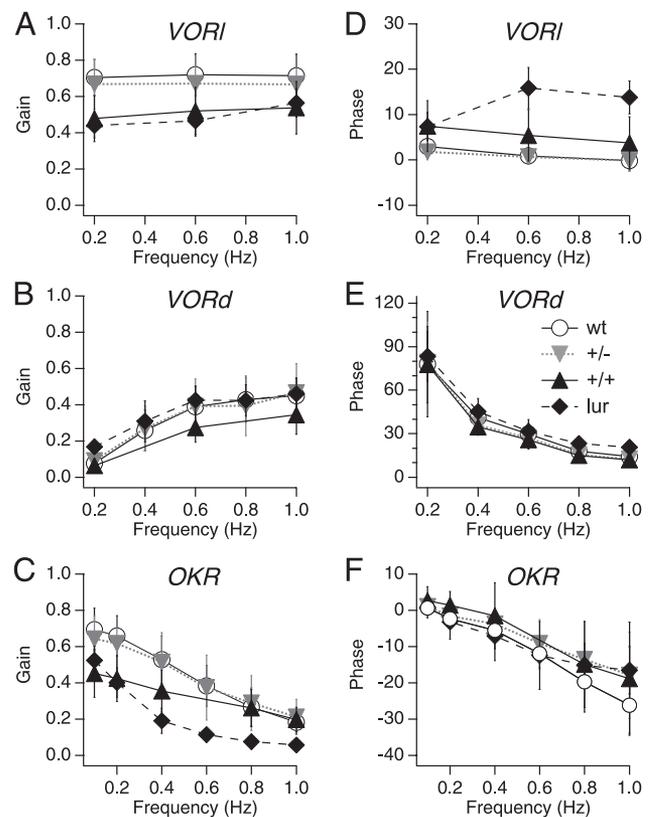

FIG. 1. Average gains and phases of the vestibuloocular reflex (VOR) in the light (VORl), the VOR in the dark (VORd), and the optokinetic reflex (OKR) are plotted vs. frequency for 4 strains of mice: wild-types ($\circ$, $n = 14$), *Lurchers* ($\blacklozenge$, $n = 9$), L7-PKCi heterozygotes ($\triangle$, $n = 9$), and L7-PKCi homozygotes ($\blacktriangle$, $n = 9$). Gain values for VORl, VORd, and OKR are plotted in A–C, respectively. Phase values for VORl, VORd, and OKR are plotted in D–F, respectively. Stimulus amplitude was fixed at $\pm 5°$. Bars indicate SDs.

($P < 0.005$) and L7-PKCi-heterozygotes ($P < 0.05$) but were normal at higher frequencies (Fig. 1C). Both L7-PKCi homozygotes and L7-PKCi heterozygotes displayed a modest phase advance in the OKR at 0.8 and 1 Hz relative to wild-type mice (Fig. 1F).

Eye movements in *Lurcher* mice were abnormal, as reported previously (van Alphen and De Zeeuw 2002). *Lurcher* mice displayed reduced VORl gains with phase advances compared with those in wild-type mice. VORl gains in *Lurcher* mice ranged from 0.44 ± 0.07 to 0.56 ± 0.08 (Fig. 1A) and phase ranged from 7.3 ± 3.1 to $13.8 \pm 3.6°$ (Fig. 1D) as stimulus frequency increased from 0.2 to 1 Hz. VORd performance was similar in *Lurcher* and wild-type mice except at 0.2 Hz at which the gain in *Lurchers* was slightly but significantly increased ($P < 0.001$). In contrast, OKR gain values were significantly decreased over the entire frequency range in *Lurcher* mice ($P < 0.001$).

Effects of unilateral vestibular damage

The ability of the mouse's oculomotor system to compensate for peripheral vestibular dysfunction was assessed by challenging mice with unilateral damage to the vestibular periphery (UVD). Mice displayed a number of postural symptoms that have been observed in other species after UVD, including head tilt, rolling, and circling. A tonic deviation of the pupil at rest

could be observed in all animals immediately after UVD. This deviation was observed in both eyes and directed toward the side of the lesion such that the ipsilateral pupil was oriented ventrotemporally and the contralateral pupil was oriented nasodorsally. The severity of this deviation varied considerably across animals. Eye position returned toward normal over a period of days, but the extent and rate of this recovery also varied from animal to animal.

Bouts of spontaneous ocular nystagmus with quick phases directed toward the intact side were prominent during the first 1–2 days after UVD. The average rates of quick phases are shown for each day relative to the UVD in Fig. 2 for wild-type mice ($n = 11$), *Lurcher* mice ($n = 7$), and L7-PKCi heterozygotes and homozygotes ($n = 6$ and 7, respectively). Pronounced variability across mice of all strains is indicated by the large error bars. Within 48 h after UVD nystagmus had recovered to control levels in all groups, but occasional bouts of nystagmus could be observed in most animals at later time points. *Lurcher* mice showed a much higher rate of spontaneous nystagmus 8 h after UVD compared with all other groups ($P < 0.05$, unpaired *t*-test), but had recovered to comparable levels by 24 h post-UVD. L7-PKCi homozygotes showed less spontaneous nystagmus prior to UVD than the other groups ($P < 0.01$) and recovered to this lower level within 3–4 days.

Responses to vestibular and visual stimulation after UVD in wild-type mice

UVD evoked rapid, adaptive plasticity in both the VOR and OKR in wild-type mice. Examples of eye movements evoked during the VORd and OKR are shown in Fig. 3, *A* and *B*, respectively, in response to rotation at 1Hz, ±5°. VORd gain decreased after UVD as expected from unilateral loss of vestibular drive and then increased over the subsequent week (Fig. 3*A*). A slow drift in evoked eye movements directed ipsiversive to the side of the lesion was evident the first day after UVD after which symmetry in oculomotor responses was largely restored. UVD also evoked increases in the gain of the OKR (Fig. 3*B*), which are partially obscured by the visually evoked nystagmus evident during the first few days after UVD but are apparent in the day 7 trace.
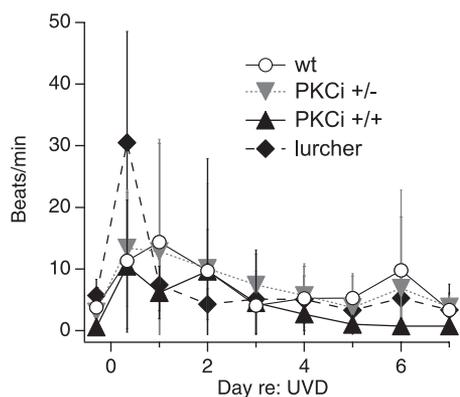

FIG. 2. Time course of nystagmus induced by unilateral vestibular damage. Average number of quick phases measured during 3 min in darkness are plotted vs. day with respect to UVD for wild-type mice (○, $n = 11$), *Lurchers* (◆s, $n = 7$), and L7-PKCi heterozygotes (△, $n = 6$) and homozygotes (▲, $n = 9$). Bars indicate SE.
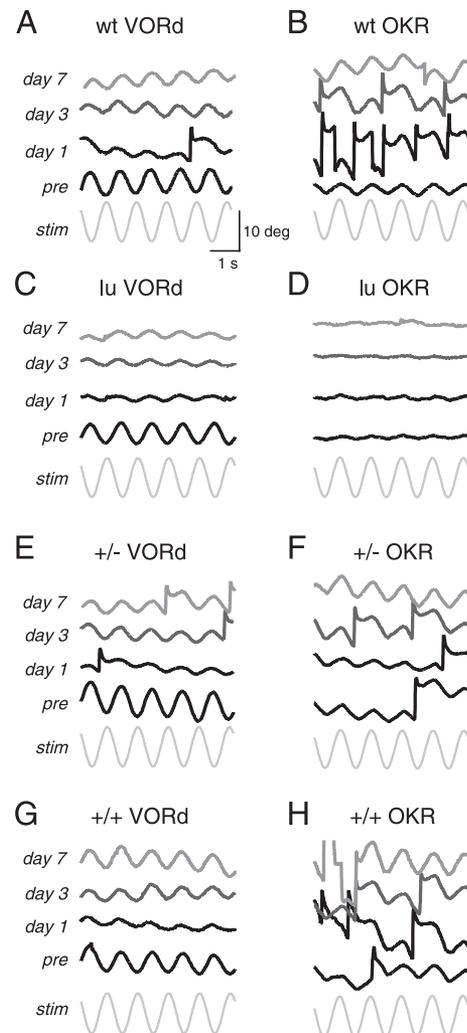

FIG. 3. Examples of eye movements evoked during the VORd (*left*) and the OKR (*right*) in wild-type, *Lurcher*, PKCi heterozygote, and PKCi homozygote mice. Stimuli were delivered at 1 Hz, ±5°; movements directed ipsiversive to the lesioned side are downward-going.

Figure 4 summarizes the effects of UVD over time on VOR and OKR in 14 wild-type mice in response to rotation with an amplitude of ±5° at 1 Hz. UVD produced an immediate decrease in VORl gain that was followed by a rapid recovery over the course of a few days (Fig. 4*A*, ○). The gain of the VORl decreased significantly to an average of 57% of control values when measured 8 h after UVD (from 0.71 ± 0.12 to 0.41 ± 0.08; $P < 0.001$). VORl gain increased over the first 3 days to 0.64 ± 0.11 (88% of control levels) and maintained this value for the 1 wk duration of the experiment. UVD induced a small phase lag in the VORl that was not significantly different from control values (Fig. 4*D*). These data indicate that in the face of unilateral loss of vestibular function, mice are able to undergo rapid and nearly complete functional recovery when provided both visual and vestibular signals.

The effects of UVD on the VORd are shown in Fig. 4, *B* and *E*. When measured at 1Hz, VORd gains in wild-type mice dropped to an average of 29% of control values (from 0.47 ± 0.16 to 0.12 ± 0.06) when measured 8 h after UVD. VORd gain increased significantly over the first 3 days post UVD to attain plateau values of 50–60% of control ($P < 0.001$) UVD
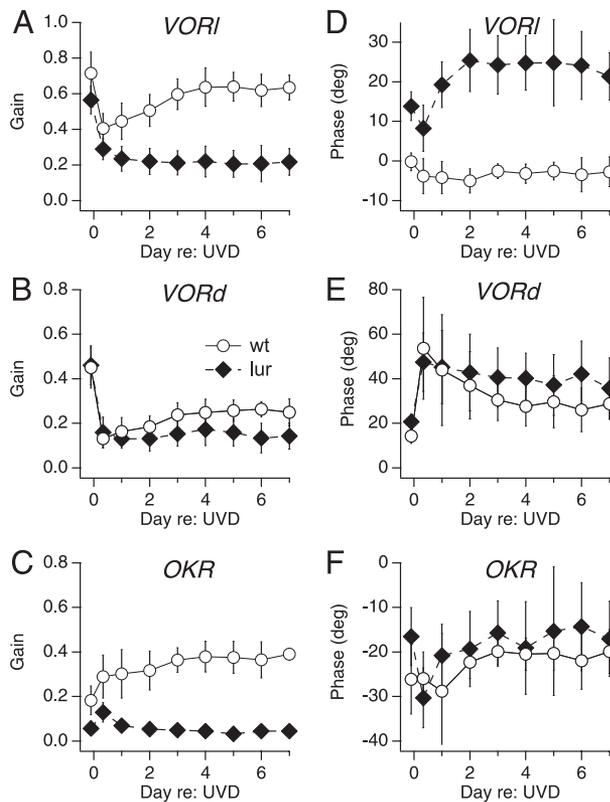
FIG. 4. Oculomotor plasticity induced by UVD in wild-type and *Lurcher* mice. *A* and *B*: gain and phase, respectively, of the VORl prior to and after unilateral vestibular damage in 14 wild-type mice (○) and 9 *Lurcher* mice (◆). The gain and phase of the VORd for the same mice are plotted in *C* and *D,* and the OKR gain and phase are plotted in *E* and *F*. Stimuli were delivered at 1 Hz, ±5°. Bars indicate SDs.

induced a large phase lead in the VORd (from $14 \pm 3°$ prior to UVD to $54 \pm 23°$ when measured 8 h post-UVD; Fig. 4*E*). Phase lead declined toward control levels over the subsequent 3 days, but remained significantly elevated relative to controls ($29 \pm 7°$ 7 days post-UVD; $P < 0.05$).

The decrease in VORd gain after UVD was accompanied by a pronounced increase in OKR gain (Fig. 4*C*). In response to optokinetic stimulation at 1 Hz, OKR gain increased significantly within 8 h of UVD, from 0.18 ± 0.06 to 0.29 ± 0.1 ($P < 0.001$). OKR gain increased further over the next few days to attain a plateau level of 0.39 ± 0.03 that was maintained for the 7 day duration of the experiment. The phase of the OKR was not significantly affected by UVD (Fig. 4*F*).

Recovery from UVD in Lurcher mice

Lurcher mice were used to test the involvement of olivo-cerebellar circuitry in oculomotor compensation for vestibular damage. Oculomotor plasticity induced by UVD was impaired severely in *Lurcher* mice. Within 8 h of UVD, the gain of the VORl decreased significantly to $52 \pm 13\%$ of control values (from 0.56 ± 0.08 to 0.29 ± 0.06; $P < 0.001$, $n = 9$; Fig. 4*A*, ◆). In contrast to wild-type mice, *Lurcher* mice exhibited no improvement in VORl gain over the subsequent week. Seven days after UVD, VORl gain remained depressed at $39 \pm 11\%$ of control levels (vs. $84 \pm 23\%$ in wild-type mice). The phase of the VORl was also impaired by UVD in *Lurcher* mice. VORl phase decreased from a $14 \pm 4°$ lead in intact *Lurcher*

mice to a $8 \pm 6°$ lead 8 h after UVD. Phase lead increased significantly to attain a plateau level of between 20 and 25° that was maintained from the 2nd through the 7th day post-UVD ($P < 0.005$; Fig. 4*D*).

The lack of functional recovery of the VORl in *Lurcher* mice could be accounted for by impairments in both VORd and OKR plasticity. Examples of eye movements evoked during the VORd and OKR in a *Lurcher* mouse are shown in Fig. 3, *C* and *D,* respectively. After UVD, the gain of the VORd in *Lurcher* mice decreased significantly to $37 \pm 7\%$ (from 0.46 ± 0.09 to 0.16 ± 0.07; $P < 0.02$) and remained at this depressed level during the duration of the experiment (Fig. 3*B*). VORd phase lead in *Lurcher* mice increased from 21 ± 3 to $48 \pm 13°$ 8 h after UVD and declined over the next 2 days to $40 \pm 11°$, remaining persistently elevated with respect to control levels ($P < 0.02$). The OKR exhibited a transient gain increase 8 h after UVD from 0.06 ± 0.01 to 0.13 ± 0.04 ($P < 0.001$). OKR gain returned to control values within 1 day of UVD (Fig. 4*C*). OKR phase lag also increased transiently 8 h after UVD but returned to control levels within a day (Fig. 4*F*). These data indicate that oculomotor plasticity induced by UVD is abnormal in *Lurcher* mice.

Recovery from UVD in PKCi mice

The comparison of *Lurcher* and wild-type mice suggest that functional cerebellar circuitry is required for the gain increases in the VORd and OKR that contribute to the rapid recovery of oculomotor function after UVD. To determine whether cerebellar LTD and PKC expression in Purkinje cells are required for these forms of oculomotor plasticity, we examined the effects of UVD on L7-PKCi transgenic mice. Examples of the VORd and OKR evoked prior and after UVD are shown in PKCi mutant mice in Fig. 3, *E–H*. Figure 5 demonstrates that oculomotor plasticity induced by UVD was intact in both L7-PKCi heterozygotes ($n = 9$) and L7-PKCi homozygotes ($n = 9$). The data plotted in Fig. 5 are normalized to control values to facilitate comparisons across different strains of mice and include data from wild-type and *Lurcher* mice normalized from Fig. 4. Eight hours after UVD, the gain of the VORl in L7-PKCi heterozygotes significantly dropped to $55 \pm 16\%$ of control levels ($P < 0.001$). Within 4 days of UVD, VORl gains were restored to $93 \pm 15\%$ of control levels (Fig. 5*A*).

Although L7-PKCi-homozygotes exhibited a significantly greater drop in VORl gains 8 h after UVD (to $37 \pm 14\%$ of control levels; $P < 0.05$), their VORl gains recovered to $92 \pm 31\%$ of control levels within 4 days of UVD. VORl phase values tended to be more variable after UVD in L7-PKCi homozygotes versus heterozygotes and wild-type mice, but VORl phase was not significantly affected by UVD in either strain of PKCi mice (Fig. 5*D*).

The effect of UVD on the VORd was indistinguishable in PKCi mutants and wild-type mice (Fig. 5*B*). Eight hours after UVD, VORd gains in L7-PKCi heterozygotes and homozygotes dropped to 30 ± 13 and $29 \pm 12\%$, respectively ($P < 0.001$ each). Within 3 days of UVD, VORd gains increased to $50 \pm 13\%$ in L7-PKCi heterozygotes and $54 \pm 18\%$ in L7-PKCi homozygotes, exhibiting no significant increases in gain during the subsequent 4 days in either strain (Fig. 5*B*). VORd phase was also similarly affected by UVD in wild-type and L7-PKCi mice (Fig. 5*E*). Directional asymmetries in eye
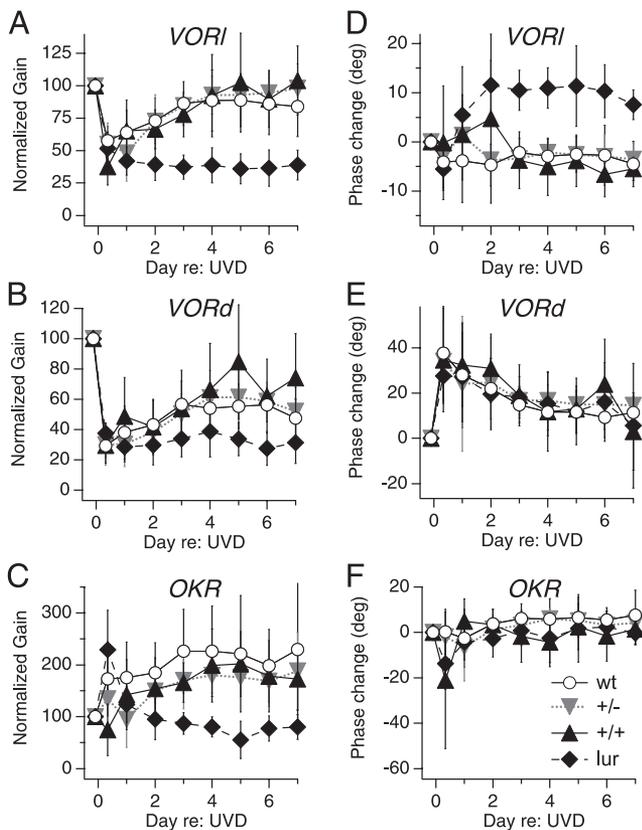
FIG. 5. Comparison of effects of UVD on oculomotor plasticity in PKCi heterozygotes and homozygotes, *Lurchers*, and wild-type mice. *A* and *B*: gain and phase, respectively, of the VORl prior to and after UVD in 9 PKCi heterozygotes (▽), 9 PKCi homozygotes (▲), 13 wild-type mice (○), and 9 *Lurcher* mice (◆). The gain and phase of the VORd for the same mice are plotted in *C* and *D,* and the OKR gain and phase are plotted in *E* and *F*. Data are normalized to the prelesion control values; data for wild-type and Lurcher mice are replotted from Fig. 4. Stimuli were delivered at 1 Hz, ±5°. Bars indicate SDs.

movement were variable across mice but tended to be largest during the first day after UVD, declining to control level within 3 days in all strains of mice ($P > 0.6$).

OKR control gains were indistinguishable in wild-type, L7-PKCi heterozygotes, and L7-PKCi homozygotes (0.18, 0.21, and 0.20, respectively). After UVD the OKR exhibited lasting increases in both wild-type and PKCi mutants (Fig. 5*C*), but the initial effects differed across genotypes. Eight hours after UVD, OKR gains significantly increased in both wild-type and PKCi heterozygote mice to 173 ± 72 and 134 ± 32%, respectively ($P < 0.001$ and $P < 0.01$, respectively). In contrast, OKR gain in L7-PKCi homozygotes mice decreased to 75 ± 50% of control levels, a value significantly lower than in wild-type mice ($P < 0.005$) and in L7-PKCi heterozygote mice ($P < 0.05$). OKR gain increased over the subsequent days in L7-PKCi homozygotes, attaining levels between 165 and 200% of control. Steady-state (4–7 days post UVD) increases in OKR gain tended to be higher in wild-type versus L7-PKCi heterozygotes and homozygotes, but these differences were not significant.

DISCUSSION

This study examined whether adaptive gain changes induced by unilateral vestibular dysfunction rely on cerebellar LTD. In

wild-type mice, UVD triggered rapid gain increases in both the VOR and OKR. Similar increases in gain were observed in LTD-deficient L7-PKCi transgenic mice that are impaired in their ability to increase VOR gain after visual-vestibular mismatch training (De Zeeuw et al. 1998; van Alphen and De Zeeuw 2002). In contrast, *Lurcher* mice did not exhibit gain increases after UVD. These findings demonstrate that peripheral vestibular damage triggers gain increases in the VOR and OKR that depend on the integrity of the olivo-cerebellar circuit but not on cerebellar LTD.

Effects of UVD in wild-type mice

The consequences of damage to the vestibular periphery have been described extensively in other species (reviewed in Curthoys and Hamalgyi 1995; Smith and Curthoys 1989). Unilateral loss of tonically firing vestibular nerve afferents produces an imbalance in the activation of central vestibular neurons, leading to slow eye movements that are interrupted by quick resetting saccades. This nystagmus has been shown to decline within 2–3 days in most species via processes that reflect CNS plasticity (Smith and Curthoys 1989). Unilateral plugging of the horizontal semicircular canal preserves vestibular nerve firing, but as with complete labyrinthectomy, canal plugging abolishes vestibular nerve responses to head motion, resulting in a significant drop in VOR gain. In the present study, mice exhibited robust decreases in gain and a prominent nystagmus during the first day after UVD, but the nystagmus was smaller in magnitude and considerably more variable than that described in other species. Our method of vestibular damage differed from a labyrinthectomy per se in that the crista was not directly removed and differed from a canal plug in that we physically damaged the semicircular canal and flushed air toward the crista. It is thus likely that the UVD in this study precluded vestibular encoding of head motion but produced relatively mild and transient impairments in spontaneous firing of vestibular afferents. Some of the increases in VOR gain after physical plugging of the semicircular canal have been attributed to peripheral rather than central processes (Hess et al. 2000). The finding that *Lurcher* mice did not show increases in VOR gain indicates that the oculomotor plasticity we measured in this study resulted from central rather than peripheral adaptive mechanisms.

Mice exhibited rapid and robust increases in VORd gain over the first 3–4 days of unilateral loss of vestibular drive induced by UVD. Similar increases in VORd gain within the first few days of vestibular damage have been observed after unilateral labyrinthectomy in monkeys (Fetter and Zee 1988), goldfish (Weissenstein et al. 1996), and gerbils (Shinder et al. 2005) as well as after canal plugging in monkeys (Paige 1985) and cats (Broussard et al. 1999). These rapid increases in gain require vision and are likely to be triggered by bilateral imbalance in head-movement drive signals rather than a lack of spontaneous firing from the vestibular nerve because they are evident after canal plugging (Fetter et al. 1988; Lasker et al. 1999, 2000; Paige 1985).

The findings on wild-type mice presented here differ quantitatively from those described in a previous study in which VORd gain increases were observed between 4 and 7 days after labyrinthectomy (Murai et al. 2004). During this period, VORd gains did not increase significantly in our study. The discrep-

ancy might reflect differences in the head-motion stimuli; the previous study used peak head-motion velocities of 120°/s, which is fourfold greater than the stimuli used in the present study. Such rapid stimuli may have activated plasticity in nonlinear VOR pathways that may follow a different time course than plasticity in the linear pathways, which operate at slower stimulus speeds (Minor et al. 1999).

As with other species, mice rely on a combination of visual and vestibular signals to generate compensatory eye movements during motion of the head. Increases in both VORd and OKR gains contributed to the nearly complete recovery of the VORl after UVD in mice. Rapid increases in OKR gain compensated for the reduced vestibular drive. Adaptive plasticity in the OKR during vestibular compensation has also been observed in monkeys, in which the initial slow phase velocity of the OKR increases after both unilateral labyrinthectomy (Fetter and Zee 1988) and canal plugging (Paige 1985).

We conclude that adaptive plasticity in both the VOR and OKR contribute to the restoration of oculomotor function following UVD in mice and that the consequences of the UVD used in this study are largely compatible with those of labyrinthectomy or canal plugging applied to other species.

VOR and OKR gain increases triggered by UVD depend on a functional cerebellum but not on cerebellar LTD

The increases in VOR gain following UVD depended on the integrity of olivo-cerebellar circuitry, as evidenced from the results in *Lurcher* mice. *Lurcher* mice have a mutation in the delta 2 glutamate receptor gene (Zuo et al. 1997), which results in postnatal Purkinje cell death and consequent degeneration of numerous cerebellar granule cells and inferior olive neurons (Caddy and Biscoe 1979). Effects of the Lurcher mutation on vestibular nucleus neurons have not been reported. However, the fact that the VORd is normal or even slightly enhanced at the lower frequencies in intact *Lurcher* mice indicates that the Lurcher mutation affected VOR plasticity via its consequences on cerebellar circuitry (see also van Alphen and De Zeeuw 2002). A critical role for the cerebellum in VOR plasticity following UVD has been described previously (Courjon et al. 1982; Johnston et al. 2002).

Although oculomotor plasticity induced by UVD requires an intact olivo-cerebellar circuit, results from PKCi mice indicate that it does not require cerebellar LTD. While heterozygous L7-PKCi mutants may exhibit a slight capacity for LTD induction that could enable these animals to compensate for vestibular damage (De Zeeuw et al. 1998), LTD stimulus protocols in homozygous L7-PKCi mutants show a potentiation of the parallel fiber to Purkinje cell synapse rather than a depression (De Zeeuw et al. 1998). The finding that vestibular compensation in the homozygous animals is comparable to that in wild types and heterozygous L7-PKCi mutants indicates that LTD is not required for adaptive gain increases evoked by UVD.

In contrast, L7-PKCi mice did not exhibit increases in VORd gain evoked during brief periods of visual-vestibular mismatch training (De Zeeuw et al. 1998), and VORd gain increases induced by eight sequential periods of such training paradigms were significantly smaller in L7-PKCi mice than in wild types (van Alphen and De Zeeuw 2002). Thus PKC expression in Purkinje cells is required for both short- and

longer-term increases in VOR gain that are induced by discrepant visual and vestibular experience in intact mice but not for long-term gain increases induced by peripheral vestibular dysfunction. Interestingly, decreases in VOR gain induced by multiple days of visual-vestibular mismatch training were normal in L7-PKCi mice, whereas phase changes evoked by this paradigm lagged significantly (van Alphen and De Zeeuw 2002). Together, these results indicate that visual experience calibrates the VOR via a number of different mechanisms and that cerebellar LTD cannot account for all forms of VOR plasticity.

Baseline oculomotor performance in homozygous L7-PKCi mice proved to be different from heterozygous mice, which were indistinguishable from wild-type mice in both this and a previous study (De Zeeuw et al. 1998). One potential explanation for the difference is that homozygous mutants show long-term potentiation (LTP) after conjunctive glutamate pulses and Purkinje cell depolarization, whereas the heterozygous mice do not (De Zeeuw et al. 1998). In principle, an increased level of LTP induction might lead to altered simple spike responses and thereby to performance deficits. Alternatively, it is possible that the elimination of the multiple climbing fiber innervation is more prominently affected in the homozygous mice than in the heterozygous mice (Chen et al. 1995; De Zeeuw et al. 1998). Such a deficit may also influence motor performance. However, despite the differences in baseline motor performance, vestibular compensation appeared equally unimpaired in both L7-PKCi groups.

The OKR increased robustly after UVD in both strains of L7-PKCi mice. In L7-PKCi homozygotes, however, the OKR gain was reduced 8 h after UVD, and OKR gain was not significantly increased in L7-PKCi heterozygotes until the second day after UVD. These results suggest that OKR plasticity depends on two mechanisms that operate in parallel, a fast mechanism that depends on PKC expression in Purkinje cells, and a PKC-independent mechanism. A role for PKC in the initial stages of vestibular compensation is supported by a number of previous studies. Rapid changes in PKC expression in cerebellar Purkinje cells have been observed after labyrinthectomy (Barmack et al. 2001; Goto et al. 1997), whereas a pharmacological blockade of PKC causes an increase in spontaneous nystagmus following labyrinthectomy in guinea pigs (Sansom et al. 2000) and delays the normally rapid recovery from nystagmus in rats (Balaban et al. 1999).

In summary, our data indicate that there must be multiple mechanisms in the neural circuits for the VOR and OKR that underlie cerebellar-dependent adaptive gain control. Both short- and long-term plasticity induced by visual-vestibular mismatch training are facilitated by PKC activation in Purkinje cells and may utilize LTD as a mechanism of learning. In contrast, plasticity following peripheral vestibular dysfunction, which is primarily a long-term process, requires the integrity of the olivo-cerebellar circuitry but proceeds independently of LTD and Purkinje cell PKC activation. Multiple sites of cellular plasticity have been postulated to contribute to cerebellar-dependent motor learning (Boyden et al. 2004; Broussard and Kassardjian 2004; Medina et al. 2000), and vestibular compensation is thought to involve a number of physiological mechanisms (Curthoys 2000; Dieringer 2003; Vibert et al. 1999). Recent findings using reversible blockade of glutamatergic trans-

mission show that the expression of short-term changes in VOR gain requires the cerebellar flocculus, whereas the expression of long-term changes do not (Kassardjian et al. 2005). Similar results were obtained for the OKR when the flocculus was reversibly silenced with lidocaine (Shutoh et al. 2006), implying that a brain stem site maintains persistent gain changes in both VOR and OKR. The current finding that gain increases following UVD depend on an intact cerebellar circuitry but not on LTD is consistent with this hypothesis. It will be intriguing to determine how different components of the circuit are responsible for plasticity that occurs over different time scales and in response to different stimulus conditions.

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