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Brief dark exposure restored ocular dominance plasticity in aging mice and after a cortical stroke

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ABSTRACT

In the primary visual cortex (V1), monocular deprivation (MD) induces a shift in the ocular dominance (OD) of binocular neurons towards the open eye (Wiesel and Hubel, 1963; Gordon and Stryker, 1996). In V1 of C57Bl/6J mice, this OD-plasticity is maximal in juveniles, declines in adults and is absent beyond postnatal day (PD) 110 (Lehmann and Löwel, 2008) if mice are raised in standard cages. Since it was recently shown that brief dark exposure (DE) restored OD-plasticity in young adult rats (PD70-100) (He et al., 2006), we wondered whether DE would restore OD-plasticity also in adult and old mice and after a cortical stroke. To this end, we raised mice in standard cages until adulthood and transferred them to a darkroom for 10–14 days. Using intrinsic signal optical imaging we demonstrate that short-term DE can restore OD-plasticity after MD in both adult (PD138) and old mice (PD535), and that OD-shifts were mediated by an increase of open eye responses in V1. Interestingly, restored OD-plasticity after DE was accompanied by a reduction of both parvalbumin expressing cells and perineuronal nets and was prevented by increasing intracortical inhibition with diazepam. DE also maintained OD-plasticity in adult mice (PD150) after a stroke in the primary somatosensory cortex. In contrast, short-term DE did not affect basic visual parameters as measured by optomotry. In conclusion, short-term DE was able to restore OD-plasticity in both adult and aging mice and even preserved plasticity after a cortical stroke, most likely mediated by reducing intracortical inhibition.

1. Introduction

Rodent V1 is dominated by input from the contralateral eye (Dräger, 1975, 1978) but MD can induce a shift in the OD of binocular neurons towards the open eye (Wiesel and Hubel, 1963; Gordon and Stryker, 1996; Cang et al., 2005a). In V1 of C57Bl/6J mice, this OD-plasticity is maximal at 4 weeks of age, declines in 2–3 month old animals and is absent beyond PD110 (Espinosa and Stryker, 2012; Levelt and Hübener, 2012), even after longer deprivation times (Greifzu et al., 2012), if animals are raised in standard cages (SC). In critical period mice (PD19-32), 4 days of MD are sufficient to induce OD-shifts towards the open eye (Gordon and Stryker, 1996). This "juvenile" OD-shift is predominantly mediated by a decrease in the cortical responses to visual stimulation of the deprived eye. In contrast, in 2–3 month old SC-raised mice, significant OD-shifts need 7 days of MD and are primarily mediated by increased open eye responses ("adult" OD-plasticity) (Sawtell et al., 2003; Hofer et al., 2006; Heimel et al., 2007; Sato and Stryker, 2008). It has been shown that the balance between excitation and inhibition is important for regulating plasticity in V1: during postnatal development, the maturation of GABAergic (γ-aminobutyric acid) circuitry opens the critical period for OD-plasticity (Huang et al., 1999, 2010; Rozas et al., 2001) and raising mice in an enriched environment (EE) both preserves a juvenile inhibitory tone and juvenile-like OD-plasticity into adulthood (Greifzu et al., 2014). While dark-rearing has been extensively studied (Hooks and Chen, 2007; Berardi et al., 2000), the effects of short periods of dark exposure (DE) during adulthood are less well understood. Recently, it was shown that 10 days of DE in PD70-100 SC-raised rats reactivated OD-plasticity in V1, reduced the level of $GABA_A$ receptors relative to AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors and caused a return to the juvenile form of NMDA (*N*-methyl-D-aspartate) receptors (He et al., 2006). We therefore wondered whether short-term DE would restore OD-plasticity in adult and old mice already beyond their sensitive phase for OD-plasticity and would also preserve OD-plasticity after a cortical stroke. Testing not only young adult but also old animals is rather important since there are

Abbreviations: DE, dark exposure; EE, enriched environment; LR, light reared; MD, monocular deprivation; OD, ocular dominance; ODI, ocular dominance index; PD, postnatal day; PNN, perineuronal net; PT, photothrombosis; PV, parvalbumin; S1, primary somatosensory cortex; SC, standard cage; V1, primary visual cortex.

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numerous age-dependent changes of cortical circuitry such as reduced functional selectivity and signal-to-noise ratio.

Thus a possible therapeutic strategy that increases cortical plasticity in young adult animals must not necessarily be effective during old age. We therefore tested the effect of brief DE on both adult and old mice. Using optical imaging of intrinsic signals, we show that 14 days of DE reactivated OD-plasticity in 4–6 month old mice after 4 and 7 days of MD. The restored OD-shift was mediated by a significant increase of open eye responses in V1 and prevented by diazepam injections. In addition, we observed a significant reduction of the number of parvalbumin expressing (PV^+) cells and perineuronal nets (PNNs) in the visual cortex of DE-mice compared to light-reared (LR) controls. Fourteen days of DE were also sufficient to restore OD-plasticity in old mice (PD535) after 7 days of MD. Finally, brief DE in adulthood (PD150) also maintained OD-plasticity after a stroke in the primary somatosensory cortex (S1). Short-term DE during adulthood did neither impair basic visual acuity nor the experience-dependent increase of visual acuity after MD as measured by optomotry (Prusky et al., 2004). Taken together, our data strongly suggest short-term DE as a highly efficient therapeutic intervention to restore plasticity in both adult and old mice and even after a cortical lesion, and that the DE-effect is most likely mediated via reduced intracortical inhibition.

2. Materials and methods

2.1. Animal treatment

All experimental procedures were approved by the local government (Niedersächsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit, registration number 33.9-42502-04-10/0326). Both male and female C57BL/6J mice from the mouse colony of the central animal facility of the University Medical Center, Göttingen (groups I–III, V–VII, see next paragraph) and 10 C57BL/6JRcc mice from the Harlan laboratories (Netherlands; group IV) were raised in SCs on a 12 h light/dark cycle (LR), with food and water available ad libitum.

2.2. Dark exposure

For short-term visual deprivation (dark exposure = DE) animals were housed in SCs placed into a scantainer (Scanbur Technology, Denmark) in a completely light-tight darkroom for 10 or 14 days.

We investigated a total of 7 different experimental groups: I) adult PD138 mice (age range PD125-157; average: PD138) received either 4 days or II) 7 days of MD after 14 days of DE; III) old PD535 mice (PD517-564) received 7 days of MD after 14 days of DE; IV) diazepam or saline-treated adult mice (PD151-157; average: PD154) received 7 days of MD after 14 days of DE as well as daily injections of diazepam/saline during the MD period; V) Chronically imaged adult mice: imaging was performed before (PD116-123; average: PD118) and after 14 days of DE and 7 days of MD (PD141-150; average: PD145); VI) young adult mice (PD57-80; average: PD72) received 4 days of MD after 10 days of DE; VII) Adult mice (PD135-165; average: PD150) received a photothrombotic (PT) lesion in S1 (sham-surgery for controls) and 7 days of MD after 14 days of DE. Experimental groups also contained equally treated light-reared (LR) control mice (groups I, II, VI) and control animals without MD (groups I, II, III, VI, VII).

2.3. Optomotry

To test whether short-term DE modified basic visual abilities, the spatial frequency threshold ("visual acuity") and contrast sensitivity of the optomotor reflex of animals from all experimental groups (except groups IV and V) were determined using the virtual-reality optomotor system (Prusky et al., 2004). Briefly, freely moving animals were exposed to moving vertical sine wave gratings of various spatial frequencies and contrasts and will reflexively track the gratings by head movements as long as they can see them. Spatial frequency at full contrast and contrast at six different spatial frequencies [0.031, 0.064, 0.092, 0.103, 0.192, 0.272 cycles/degree (cyc/deg)] were varied by the experimenter until the threshold of tracking was determined.

2.4. Monocular deprivation (MD)

According to already published protocols, we always sutured the right eye of our mice (Gordon and Stryker, 1996; Cang et al., 2005a; Lehmann and Löwel, 2008) to trigger visual plasticity. DE-mice were transported (immediately after DE) in a light-tight box to the surgical suite and MD-surgery started directly to minimize light exposure after DE. After box-anesthesia with 2% isofluorane in a 1:1 mixture of nitrous oxide (N_2O) and oxygen (O_2), anesthesia was maintained with 1.5% isoflurane, lid margins were trimmed and an antibiotic gel (gentamicin gel) was applied. The eye was closed with two mattress sutures. After MD, the mice were returned to their standard home cages and stayed in normal 12 h light/dark conditions. Animals were checked daily to make sure that the eye remained closed.

2.5. Surgical preparations for optical imaging (Kalatsky and Stryker, 2003; Cang et al., 2005a)

Mice were initially box-anesthetized with 2% halothane in a 1:1 mixture of O_2:N_2O and received atropine (Franz Köhler, 0.3 mg, subcutaneously (s.c.)), dexamethasone (Ratiopharm, 0.2 mg, s.c.), and chlorprothixene (Sigma, 0.2 mg, intramuscularly). Mice were placed in a stereotaxic frame and anesthesia was maintained with 0.6–0.8% halothane in a 1:1 mixture of O_2:N_2O applied through a tube attached to the nose. Body temperature was maintained at 37 °C and the heart rate was monitored throughout the experiment. Lidocaine (2% xylocaine jelly) was applied locally to all incisions. The skin above the skull was incised to expose V1 of the left hemisphere and agarose (2.5% in 0.9% NaCl) and a glass cover-slip were placed over the exposed area. Imaging was performed through the skull. Mouse visual cortical responses were recorded using the imaging method developed by Kalatsky and Stryker (2003) and optimized for the assessment of OD-plasticity (Cang et al., 2005a). In this method, a temporally periodic stimulus is continuously presented to the animal and the cortical responses at the stimulus frequency are extracted by Fourier analysis. Optical images of intrinsic cortical signals were obtained using a CCD (charge-coupled device) camera (Dalsa) controlled by custom software. The surface vascular pattern and intrinsic signal images were visualized with illumination wavelengths set by a green (550 ± 10 nm) or red (610 ± 10 nm) interference filter, respectively. After acquisition of a surface image, the camera was focused 600 μm below the cortical surface. An additional red filter was interposed between the brain and the CCD camera. Frames were acquired at a rate of 30 Hz, temporally binned to 7.5 Hz and stored as 512 × 512 pixel images after spatial binning of the camera image. Drifting horizontal bars (2° wide) were presented to the animal at a distance of 25 cm on a high refresh-rate monitor. The distance between 2 bars was 80° and they were presented at a temporal frequency of 0.125 Hz. The visual stimulus was restricted to the binocular visual field of the left V1 (−5° to +15° azimuth) and animals were stimulated through either the left or the right eye in alternation to assess the OD of the left hemisphere. To assess map quality the stimulus monitor was placed in the right visual field of the animal at a distance of 25 cm with its left edge approximately aligned to the animal to optimally stimulate the right eye (contralateral to the recorded hemisphere). The drifting bars (elevation or azimuth) were shown across the full screen.

2.6. Data analysis

Visual cortical maps were calculated from the acquired frames by Fourier analysis to extract the signal at the stimulation frequency using custom software (Kalatsky and Stryker, 2003). While the phase