Current Biology, Vol. 15, 2119–2124, December 6, 2005, ©2005 Elsevier Ltd All rights reserved. DOI 10.1016/j.cub.2005.10.045

A Role for Retinal Brain-Derived Neurotrophic Factor in Ocular Dominance Plasticity

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Summary

Visual deprivation is a classical tool to study the plasticity of visual cortical connections. After eyelid closure in young animals (monocular deprivation, MD), visual cortical neurons become dominated by the open eye, a phenomenon known as ocular dominance (OD) plasticity [1]. It is commonly held that the molecular mediators of OD plasticity are cortically derived and that the retina is immune to the effects of MD [2–4]. Recently, it has been reported that visual deprivation induces neurochemical, structural, and functional changes in the retina [5–7], but whether these retinal changes contribute to the effects of MD in the cortex is unknown. Here, we provide evidence that brain-derived neurotrophic factor (BDNF) produced in the retina influences OD plasticity. We found a reduction of BDNF expression in the deprived retina of young rats. We compensated this BDNF imbalance between the two eyes by either injecting exogenous BDNF in the deprived eye or reducing endogenous BDNF expression in the nondeprived eye. Both treatments were effective in counteracting the OD shift induced by MD. Retinal BDNF could also influence OD distribution in normal animals. These results show for the first time that OD plasticity is modulated by BDNF produced in the retina.

Results

It is known that the expression of BDNF in the retina is dependent on visual input [6, 7]. Recently, we and others have demonstrated that both endogenous and exogenous BDNF is transported anterogradely by retinal ganglion cells (RGCs) and released to geniculocortical cells [8–10]. The activity-dependent expression of BDNF and its anterograde trafficking prompted us to investigate whether retina-derived BDNF might play a role in OD plasticity.

First, we assessed whether a brief period of MD at postnatal day 22–23 (P22–P23) modulates BDNF expression in the retina. Rats were monocularly deprived for one week, and retinal BDNF levels were measured by the enzyme-linked immunoadsorbent assay (ELISA). We observed a consistent reduction of BDNF concentration in the retinas dissected from deprived eyes with respect to control conditions. The mean BDNF concentration in retinas of deprived eyes was 3.58 ± 0.27 (S.E.) pg/mg of proteins, whereas in the retinas dissected from the open eyes, it was 6.36 ± 0.28 (S.E.) pg/mg. In normal animals, the mean concentration was 6.69 ± 0.44 (S.E.) pg/mg total protein (one-way ANOVA, $p < 0.001$; post hoc Tukey test, deprived versus open eye, $p < 0.05$) (Figure 1).

The finding of a decreased BDNF expression in the deprived retina led us to investigate whether a compensation of BDNF imbalance between the two eyes could affect the shift in cortical OD after a period of monocular occlusion. We modulated the levels of BDNF expression in the retina by using two complementary strategies. In a group of monocularly sutured animals, we increased BDNF availability to the deprived eye by intravitreally injecting recombinant BDNF. As shown in Figures 1B–1C, exogenous BDNF is efficiently taken up by the retina and transported to the lateral geniculate nucleus with a maximal accumulation at 48 hr after injection. In a second set of experiments, we decreased BDNF expression in the nondeprived eye by injecting antisense oligonucleotides against BDNF. This antisense strategy is very efficient in suppressing BDNF protein levels in the retina and BDNF anterograde transport (Figures 1D–1E and [9]). Our data demonstrate that either exogenous BDNF administration to the deprived eye or reduction of BDNF levels in the open eye impair the expected OD shift in the cortex.

Exogenous Supply of BDNF into the Deprived Eye Prevents MD Effects

6 hr before eyelid suture, P22–P23 rats (n = 6) were injected with 10 μg of recombinant human BDNF. After 3–4 days of MD, we performed extracellular recordings of single-unit activity in the primary visual cortex contralateral to the deprived eye to assess the OD of visual cortical neurons. We found that 3–4 days of MD in our control animals (n = 5, MD control) were sufficient to induce a shift of OD distribution toward the open eye (Figure 2A), as it has been shown previously [11]. In contrast, a single intravitreal injection of BDNF counteracted the MD effects on the OD distribution (χ^2 test, MD + BDNF versus MD control, $p < 0.001$) (Figure 2B). The OD distributions of all animals in each group are summarized in Figure 2D by showing the contralateral bias index (CBI), in which 0 represents complete ipsilateral dominance, and 1 indicates complete contralateral dominance. The means of the CBIs calculated for animals treated with exogenous BDNF (0.50 ± 0.019) and for the MD control group (0.36 ± 0.013) were found to be significantly different (t test, $p < 0.001$). An alternative and finer comparison

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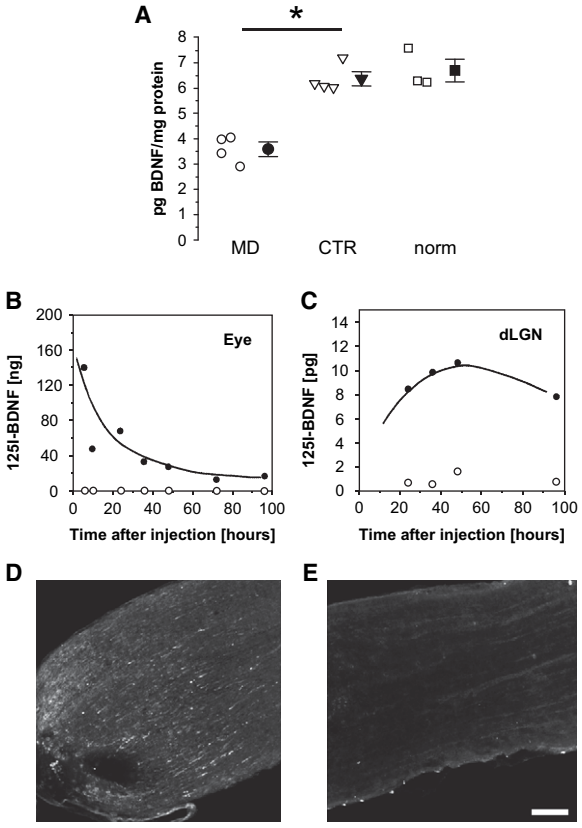

Figure 1. Modulation of Retinal BDNF Levels and BDNF Anterograde Transport

(A) Retinal BDNF expression is reduced in monocularly deprived animals. BDNF protein levels were determined by ELISA, and the concentration of BDNF protein is shown in picogram BDNF per miligram total protein. Retinas were dissected from deprived (MD, n = 4 samples of 14 retinas each) and nondeprived eyes (CTR, n = 4 samples of 14 retinas each) of animals monocularly deprived for one week and from animals reared with normal visual experience (norm, n = 3 samples of 15 retinas each). Solid symbols are mean ± S.E. The concentration of BDNF in deprived retinas is significantly reduced with respect to both nondeprived and normal retinas (one-way ANOVA, $p < 0.001$; post hoc Tukey test, $p < 0.05$). The experiment was repeated three times with different sets of samples and gave identical results.

(B and C) Measurements of radiolabeled BDNF in the eye (B) and geniculate (C) of P21 rats by γ counting after intraocular injection of 500 ng radiolabeled BDNF. Data points are from individual animals or represent the average from two independent experiments. (B) shows retention of BDNF in the injected right eye (black dots) compared with amounts of radiolabeled BDNF in the contralateral (left) eye (open circles). The levels of exogenous BDNF in the eye dropped from about 150 ng at 6 hr to about 70 ng at 24 hr and about 15 ng at 96 hr. Approximately half of the total amount in the eye was present within the retina (data not shown). (C) shows accumulation of radiolabeled BDNF in the left (black dots) and right (control) lateral geniculate nucleus (dLGN) after injection in the right eye.

(D and E) Intraocular injection of antisense, but not sense, oligonucleotides against BDNF abrogates BDNF anterograde transport. Longitudinal optic nerve sections from P24 rats which received an intravitreal injection of sense (D) or antisense oligonucleotides (E) and whose optic nerves were crushed. Immunostaining for BDNF shows BDNF accumulation at the proximal site of the crush in the sense-treated animal (D) but not in the antisense-treated one (E). The scale bar represents 100 μm.

of the OD distributions was provided by the computation of the OD score for all cells recorded in BDNF-treated and control MD animals [11, 12]. The cumulative distribution of the OD score in BDNF-treated animals was statistically different with respect to that in MD control animals (Kolmogorov-Smirnov [K-S] test, $p < 0.001$) (Figure 2E).

Reduction of BDNF Expression in the Nondeprived Eye Prevents MD Effects

We decreased BDNF expression in the nondeprived eye by injecting antisense oligonucleotides, which prevent translation of BDNF mRNA. Intraocular injections of antisense oligonucleotides against BDNF were performed every 48 hr in the nondeprived eye of P22 rats (n = 7) starting at the time of MD. Sense oligonucleotides were injected with the same time schedule and used as controls (n = 5, MD control). After 3–4 days, we recorded single-unit activity in the visual cortex contralateral to the deprived eye. Inhibition of BDNF expression in the retina by the antisense oligonucleotides almost completely prevented the effects of MD on the OD distribution as shown in Figure 2C (χ^2 test, MD + antisense versus MD control, $p < 0.001$). The mean CBI value and the cumulative distribution of the OD score derived from the MD + antisense rats were significantly different from those of MD control animals (Mann-Whitney rank sum test, $p = 0.005$, and K-S test, $p < 0.001$, respectively), but they were superimposable to those of MD rats treated with exogenous BDNF (Mann-Whitney rank sum test, $p > 0.05$, and K-S test, $p > 0.05$) (Figures 2D and 2E). Altogether, these data show that compensating the imbalance of BDNF in the retina prevents the OD shift in MD rats.

An Imbalance of BDNF between the Two Eyes Shifts OD in Rats Reared with Normal Visual Experience

We next asked whether manipulating retinal BDNF levels could shift the normal OD of cortical neurons. To address this question, we injected exogenous BDNF into one eye and antisense oligonucleotides for BDNF into the other eye in animals reared with normal visual experience. This protocol was chosen to maximize BDNF imbalance between the two eyes. The injections were repeated every 48 hr starting at P22–P23, and after 1 week, we assessed OD in the cortex ipsilateral to the BDNF-treated eye (n = 4 animals). To control for possible changes in eye preference because of physical damage or oligonucleotide delivery to the eye, we subjected seven animals to monocular, repeated intravitreal injections of sense oligonucleotides over a 7 day period. We found that repetitive injections of the sense oligonucleotides did not induce changes in OD. Indeed, the CBIs values in the sense group were identical to those in normal untreated animals (Figure 3A) (t test, $p = 0.99$). Conversely, exogenous supply of BDNF into one eye combined with antisense treatment of the other eye resulted in a consistent OD shift as demonstrated by statistical analysis of the CBI values (t test, $p < 0.001$) (Figure 3A) and of the cumulative distributions of the OD score (K-S test, $p < 0.001$) (Figure 3B). These data indicate that a modulation of retinal BDNF levels can influence the normal OD distribution in visual cortex.

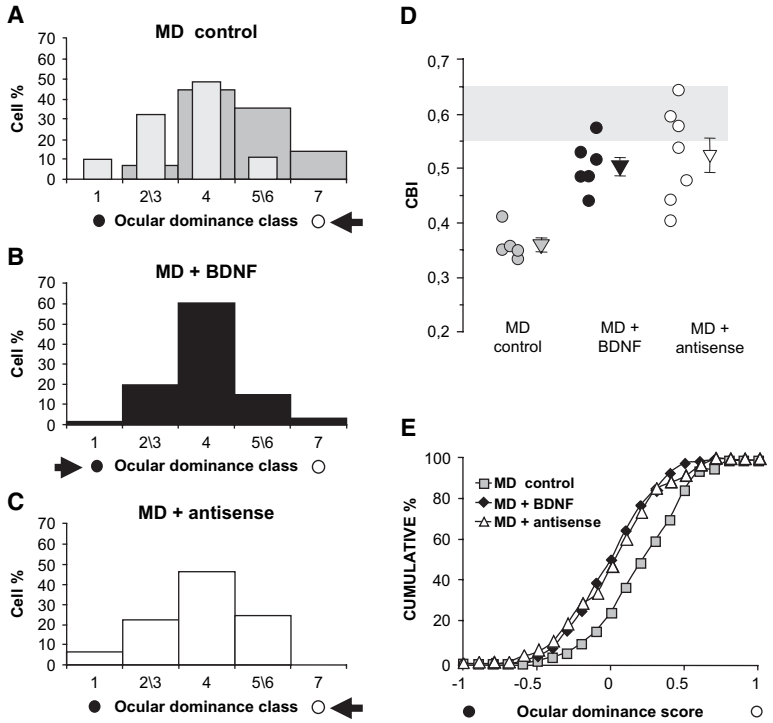

Figure 2. Retinal BDNF Affects the OD Shift Induced by MD

(A, B, and C) OD distributions of rats (P27–P28) monocularly deprived (MD) for 3–4 days and injected with: (A) sense oligonucleotides in the nondeprived eye (indicated by the arrow) (dark gray bars, n = 5 rats, 151 cells)—the light gray bars represent the OD distribution of animals reared with normal visual experience (n = 6 rats, 217 cells); (B) exogenous BDNF in the deprived eye (indicated by the arrow) (n = 6 rats, 187 cells); and (C) antisense oligonucleotides for BDNF in the nondeprived eye (indicated by the arrow) (n = 7 rats, 204 cells). The OD distributions of MD + BDNF and MD + antisense rats differ significantly from that of MD control rats (χ^2 test, $p < 0.001$).

(D) CBIs of all treated animals. Triangles represent mean CBI ± S.E.; each circle represents CBI of a single animal. The CBIs of MD + antisense and MD + BDNF rats are statistically different from those of MD control rats (Kruskal-Wallis one-way ANOVA, $p = 0.008$; post hoc Dunn's test, $p < 0.05$). Shaded region represents the CBI range of normal animals.

(E) Cumulative distribution of the OD score in each experimental group. Statistical comparison of the cumulative distributions of the OD score confirms that either antisense or BDNF treatment prevents MD effects (K-S test, $p < 0.001$).

Manipulation of BDNF Expression in the Retina Does Not Affect Visual Responses of Retinal Ganglion Cells and Geniculate Neurons

It might be argued that the effects of retinal BDNF on cortical OD are secondary to an alteration of neural activity in the afferent pathway to the cortex. To address this issue, we analyzed RGC spiking activity by extracellular recordings from the optic tract contralateral to the injected eye in a subset of antisense-, sense-, or exogenous BDNF-treated rats (n = 5–8 animals per group). BDNF-treated rats were analyzed either within 2 hr (to assess acute effects of BDNF on RGC activity) or 1–2 days after a single intravitreal injection of the neurotrophin. The injections of antisense oligonucleotides (or sense oligonucleotides as control) were repeated after 48 hr, and recordings were performed 3–4 days after beginning of the treatment. We found that the rate of spontaneous discharge of RGCs was undistinguishable between normal rats and rats receiving BDNF, antisense, or sense treatment (one-way ANOVA on ranks, $p = 0.10$) (Figures 4A and 4B). Responses to light were also similar among the groups (one-way ANOVA on ranks, $p > 0.05$) (Figures 4A and 4C).

Because BDNF is anterogradely transported, it might also affect electrical activity at the geniculate level. Accordingly, we also performed single-unit recordings from the geniculate contralateral to the injected eye in rats of the various experimental groups. To quantify cell responsiveness to visual stimulation, we computed for each geniculate cell the peak-to-baseline ratio, i.e., the ratio between peak firing rate in response to an optimal stimulus (a light bar drifting into the receptive field

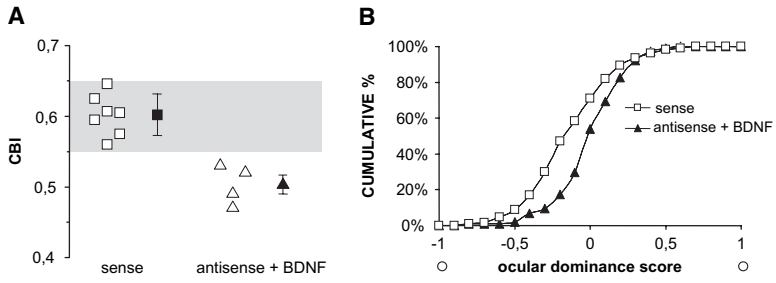

Figure 3. Retinal BDNF Influences the OD Distribution of Animals Reared with Normal Visual Experience

(A) CBIs of normally reared rats that received monocular injections of sense oligonucleotides (sense) or injections of exogenous BDNF into one eye and antisense oligonucleotides for BDNF into the other eye (antisense + BDNF). Solid symbols represent mean CBI ± S.E.; each open symbol represents CBI of a single animal. Imbalance of BDNF levels between the two eyes causes a statistically significant OD shift (t test, $p < 0.001$). Shaded region represents the CBI range of normal animals.

(B) Cumulative distributions of the OD score in the treated animals. Statistical testing confirms that the combined treatment with antisense in one eye and BDNF in the other eye affects eye preference of cortical neurons (K-S test, $p < 0.001$).

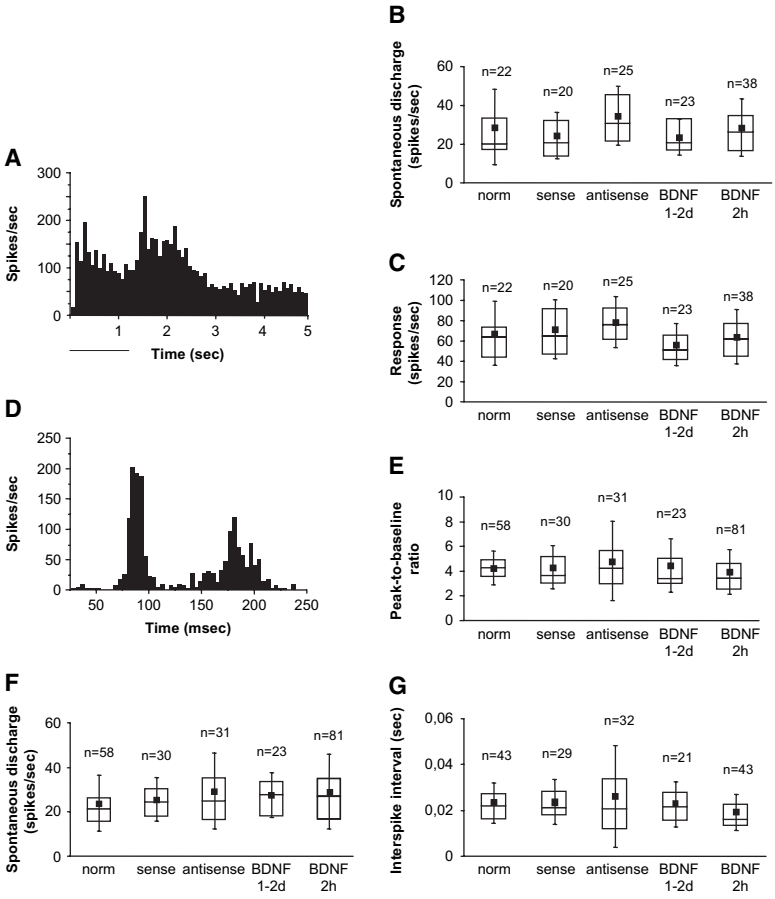

Figure 4. Functional Properties of RGCs and Geniculate Neurons Are Not Affected by Manipulation of Retinal BDNF Levels

(A–C) RGC spiking activity recorded in the optic tract in response to a light flash. A representative ON-OFF response is shown in (A). The bar underneath the peristimulus time histograms (PSTH) represents flash duration. (B and C) Box charts showing RGC spontaneous discharge and average response to light in normal uninjected rats (norm) and rats injected with sense oligonucleotides (sense), antisense oligonucleotides (antisense), and exogenous BDNF (1–2 days and 2 hr after treatment). Mean spontaneous firing rate was quantified in the 3–5 s interval of each PSTH. Response was taken as the average spike activity in the 0–2.5 s interval, including both the ON and the OFF response activity in each graph. Statistical analysis demonstrates that baseline activity and average response are superimposable among the groups (one-way ANOVA on ranks, $p > 0.05$).

(D) Representative response of a geniculate cell to the presentation of a sinusoidal grating (spatial frequency 0.07 cycles/deg, contrast 80%, temporal frequency of alternation 4 Hz). The cell shown here exhibits nonlinear spatial summation.

(E–G) Box plots summarizing the distribution of the peak-to-baseline ratio (E), spontaneous discharge (F), and interspike intervals (G) for cells recorded in the geniculate of normal rats and rats injected with sense oligonucleotides, antisense oligonucleotides, or exogenous BDNF. For each box chart, the central horizontal line is the median value, and the other two horizontal lines are 25% and 75% interquartile ranges; the open square is the mean value, and the vertical bars are the standard deviations. No statistical differences can be detected among the experimental groups (one-way ANOVA on ranks, $p > 0.05$).

or an alternating sinusoidal grating) (see Figure 4D) and the rate of spontaneous discharge. We found that peak-to-baseline ratios were identical in sense, antisense, or BDNF-treated animals as shown in Figure 4E (one-way ANOVA on ranks, $p = 0.13$). Spontaneous discharge was also superimposable among the experimental groups (one-way ANOVA on ranks, $p = 0.13$) (Figure 4F). Analysis of interspike interval distributions revealed no differences in the temporal patterning of the discharge between the various groups (one-way ANOVA on ranks, $p = 0.15$) (Figure 4G). Thus, our analysis revealed no significant differences in visual responses and baseline activity among the different injection conditions.

To further determine stimulus selectivity after the various treatments, we recorded responses of geniculate cells to sinusoidal gratings alternating at different temporal frequencies (see Figure 4D). No differences in the shape of the temporal frequency tuning curve were observed among the experimental groups (two-way ANOVA, $p > 0.05$). Most units responded best to temporal frequencies around 4 Hz and showed a drop off in response amplitude at higher and lower temporal frequencies (data not shown). We also found that the spatial frequency tuning characteristics of geniculate cells was similar in all experimental groups. Most cells showed maximal responses at 0.07 cycles/deg and sharp declines in sensitivity at higher spatial frequency with cut offs in the order of 0.35 cycles/deg. Finally, contrast response characteristics were also superimposable among the groups (data not shown). Overall, we conclude that the different injection conditions produced no detectable differences in input activity that might impact on OD at the cortical level.

Discussion

Our results show for the first time that OD plasticity in the primary visual cortex is influenced by BDNF expression in the retina. Indeed, we demonstrate that monocular eyelid suture decreases BDNF levels in the deprived eye and that a compensation of this BDNF imbalance, via BDNF injections into the deprived eye or antisense injections into the open eye, counteracts the effects of MD. Modulation of retinal BDNF levels induces a small OD shift also in normally reared animals. These plastic effects are not accompanied by measurable alterations in electrical activity in the afferent pathway to the cortex, suggesting that some aspect of BDNF signaling other than input activity is important.

Lack of visual experience during a developmental critical period is well known to alter the anatomical and physiological properties of the visual cortex [1]. The mechanisms underlying these plastic events are still debated, but the general consensus is that their locus is cortical. In particular, the retina has long been considered virtually unaffected by visual deprivation. Indeed, early experiments performed mainly on the cat visual system found no discernible effects of visual deprivation on either retinal morphology or physiology [2, 13, 14]. These findings have suggested a central origin for the functional abnormalities of visually deprived animals. More recently, however, it has been possible to detect alterations of retinal circuitry in animals deprived of visual experience [5]. Specifically, the developmental segregation of RGC dendrites into ON or OFF sublamina and the emergence of pure ON versus OFF responses are blocked by dark rearing [5]. Whether these alterations at the retinal level contribute to experience-dependent changes in primary visual cortex remains unknown. Neurochemical alterations in the retina have also been reported after manipulation of visual experience. Both BDNF mRNA and protein levels are increased by rearing rats in constant light and decreased by dark rearing [6]. We have shown here that deprivation of patterned stimulation by MD is sufficient to halve BDNF protein levels in the sutured retina. Our findings are in keeping with those of Seki and colleagues [7] who reported a reduction of BDNF expression in the retina of rats monocularly deprived for two weeks after eye opening. To test whether altering retinal BDNF levels may have an impact on the outcome of MD, we injected recombinant BDNF into the deprived eye or antisense oligonucleotides for BDNF into the open eye, and we measured the OD shift after 3–4 days of MD. As a result of both treatments, the effect of MD was to a large extent prevented.

Methodological Considerations

Our measurements of radiolabeled BDNF after intravitreal delivery of microgram amounts indicate that the eye retains tens of nanograms of BDNF protein 24 hr after injection (see Figure 1B). Because endogenous BDNF amounts in the postnatal rodent retina are in the order of a few picograms (Figure 1A and [15]), BDNF levels were approximately 10,000-fold higher in the injected retina than normal. Thus, if an imbalance of BDNF levels between the two eyes controls eye preference, one might expect a paradoxical shift in OD in favor of the deprived, BDNF-injected eye in monocularly deprived animals. However, we observed only a compensation of the OD shift after BDNF administration to the sutured eye but not an "overcorrection." This finding can be explained by the fact that uptake and anterograde transport of exogenous BDNF are largely receptor mediated and saturate with much lower amounts of injected BDNF [16, 17]. Indeed, only a few picograms of BDNF are anterogradely transported to the dLGN after injection of 0.5–1 μg into the eye (Figure 1C). Thus, saturation of uptake/transport mechanisms effectively limits the amount of exogenous BDNF that is available to RGCs and geniculate neurons.

To reduce BDNF expression in the retina, we used injection of antisense oligonucleotides that selectively target BDNF mRNA but not other neurotrophins as shown by BLAST analysis. This antisense strategy efficiently blocks BDNF synthesis and anterograde transport along the optic nerve (Figures 1D–1E and [9]). We have demonstrated in a preceding paper that intravitreal delivery of these antisense oligonucleotides decreases retinal BDNF levels with no adverse effect on RGC survival, soma size, and dendritic arborisation [9]. Intraocular injection of sense oligonucleotides had no effect on the eye preference of cortical neurons, ruling out any toxic effect of the oligonucleotide treatment per se. The finding that raising BDNF levels via exogenous administration produces OD changes that are opposite to those obtained with knockdown of BDNF further supports the specificity of our antisense approach.

Mechanisms of BDNF Action

BDNF has been reported to exert a rapid and long-lasting modulation of synaptic transmission in several studies [18, 19]. Accordingly, one possible explanation of our results is that retinal BDNF controls OD by modulating the level and/or pattern of neuronal activity along the afferent pathway to the cortex. Retina-derived BDNF might affect electrical activity both at the retinal and geniculate level because of its anterograde actions. Therefore, we have analyzed spike activity of both RGCs and geniculate neurons in rats treated with exogenous BDNF and antisense oligonucleotides. Recordings were performed either within 2 hr or 1–2 days after injection of BDNF to evaluate acute and long-term effects of the neurotrophin on neuronal firing and 3–4 days after repeated delivery of antisense oligonucleotides to assess cell excitability at the time of maximal depletion of endogenous BDNF. Indeed, since antisense oligonucleotides only prevent translation of BDNF mRNA, significant reductions of BDNF protein levels are likely to require several hours after antisense delivery, consistent with previous data [9, 20, 21]. Our data indicate that input activity is not affected by manipulation of retinal BDNF levels. Indeed, quantification of baseline activity and response properties of RGCs and geniculate cells revealed no significant differences with respect to the control animals. It is worth noting that exactly the same kind of analysis readily detected activity changes when much greater amounts of BDNF were administered into the cortex [22]. Thus, effects of retinal BDNF on OD are not secondary to discernible changes in input activity.

Although the experiments reported here indicate that at least part of the MD effect in the cortex can be attributed to changes of BDNF concentration in the eye, they do not provide a mechanism by which retinal BDNF can affect cortical plasticity. One first hypothesis is that BDNF produces changes in retinal circuitry that secondarily affect cortical OD. As discussed above, whether retinal alterations can contribute to cortical plasticity has not been demonstrated yet. A second hypothesis is that BDNF influences plasticity via an anterograde effect from the eye. This anterograde action is supported by our data demonstrating robust accumulation of BDNF in the geniculate after eye injections (see Figure 1C). Indeed, it is known that anterograde BDNF activates signal transduction cascades in geniculocortical cells and that these signaling pathways influence

several physiological processes [23, 24]. Thus, the trophic action of anterograde BDNF on thalamic cells may allow sparing of geniculocortical arbors and synaptic contacts from the deprived visual input. Indeed, there is evidence in the literature that application of a neurotrophic factor to the soma can influence axonal arborization and synapse formation [25]. In addition, BDNF released at the thalamic level might regulate synaptic transmission at geniculo-cortical synapses. It has been previously shown that stimulation of the cell body with a growth factor anterogradely regulates release probability at the synaptic terminal [23, 26]. A third hypothesis could be that retina-derived BDNF is transferred by transcytosis to cortical neurons. We have addressed this possibility by injection of iodinated BDNF into the eye followed by γ counting and autoradiography of cortical tissue, and we have found that the transport of exogenous BDNF from the retina to the cortex is below the limit of detection (see Figure S1). The minimal amount of cortically transported BDNF, which might have escaped detection, is unlikely to have any significant physiological effect given the relatively high levels of endogenous BDNF expression in the cortex. Thus, retina-derived BDNF most likely affects cortical OD plasticity by acting at the level of the geniculate neurons.

Conclusion

We have provided evidence that BDNF produced in the retina contributes to plasticity in the visual cortex after monocular deprivation. These data challenge the commonly held view that OD plasticity is exclusively attributed to cortical mechanisms.

Supplemental Data

Supplemental Data include detailed Experimental Procedures and a figure and can be found with this article online at http://www.current-biology.com/cgi/content/full/15/23/2119/DC1/.

Acknowledgments

This work was supported by Fondo per Gli Investimenti della Ricerca di Base project RBNE 01R7H4-002, by Cofinanziamento Progetti di Ricerca di Interesse Nazionale 2001 and 2002, and by National Institutes of Health grant EY 12841 (to C.S.v.B.). The authors thank Amgen for kindly supplying recombinant human BDNF and Qiao Yan and Robert Rush for the generous supply of antibodies. We are grateful to E. Putignano, A. Viegi, C. Rossi, and S. Chierzi for participating in some experiments. We thank G.M. Ratto, N. Berardi, and T. Pizzorusso for critical reading of this manuscript and C. Orsini, G.C. Cappagli, and S. Vella for invaluable technical assistance.

Received: March 8, 2005
Revised: September 12, 2005
Accepted: October 13, 2005
Published: December 5, 2005

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