Visual System Plasticity Begins in the Retina

Visual experience is known to induce developmental plasticity in visual cortex; now, Tian and Copenhagen report that experience regulates the development of retinal circuitry itself. Both pruning of retinal ganglion dendrites into ON or OFF sublamina and the emergence of pure ON versus OFF responses require visual experience.

Visual deprivation by dark rearing is a standard manipulation for studying experience-dependent development of circuitry and maps in visual cortex. Interpretation of these experiments relies on the assumption that these manipulations do not induce plasticity in the retina or the lateral geniculate nucleus of the thalamus (LGN), the two processing centers that relay visual information to cortex, but only in the cortex itself.

In this issue of *Neuron*, Tian and Copenhagen (2003) use a dark-rearing paradigm to test whether visual experience is required for maturation of receptive field properties and dendritic arborization of mouse retinal ganglion cells (RGCs). For dark rearing, animals were kept in a completely dark environment beginning at postnatal day 0 (P0), long before the earliest age of light responses in mice (P8–10, which is 3–4 days before eye opening). They focus on how dark rearing affects one feature of RGC function—ON versus OFF responsiveness (see Figure 1). Separate RGC classes respond to the onset of light (ON responses), the cessation of light (OFF responses), or both (ON-OFF responses). These receptive field classifications correlate with RGC dendritic stratification. Dendrites of ON RGCs stratify in the sublamina b of the inner plexiform layer, where they receive inputs from ON cone bipolar cells; OFF RGCs stratify in sublamina a, where they receive input from OFF cone bipolar cells, and ON-OFF RGCS are bistratified, meaning that they extend dendrites into both ON and OFF sublaminae. Independent ON and OFF channels are maintained at the level of the LGN but then converge onto layer 4 cells of the primary visual cortex. These segregated channels are important for several aspects of visual processing, including the synthesis of orientation tuning in primary visual cortex (Reid and Alonso, 1995).

Tian and Copenhagen use both a physiological and morphological approach to characterize the effects of dark rearing on the maturation of ON and OFF RGCs. First, they used multielectrode array recordings to characterize the development of receptive field properties of individual RGCs. They showed that at P10, 76% of recorded RGCs have robust ON-OFF responses. At P27–30, this percentage dropped dramatically to 21% of recorded RGCs. In mice that were dark reared from P0 to P27, the percentage of ON-OFF RGCs remained high at 82%, indicating that this reduction is mediated by visual experience.

To determine if the changes in receptive field properties correlated with changes in the dendritic stratification of RGCs, Tian and Copenhagen took advantage of a transgenic mouse that expresses YFP in several classes of RGCs under control of a Thy-1 promoter. Using confocal reconstructions, they demonstrated that in animals with normal visual experience, the number of labeled RGCs that have bistratified dendrites is reduced from 53% to 29% between P10 and P30. Thy1-YFP mice that were dark reared still had 53% bistratified cells at P30, indicating that visual activity is required for the pruning of RGC dendrites. Together with the multielectrode array recordings, these findings quite dramatically show that altered visual experience can affect retinal structure and function.

Though both multielectrode array recording and visualization of RGC dendrites in the Thy1-YFP mice allow for the sampling of many different RGC classes, these techniques have different sampling biases (as discussed extensively by the authors) which may account for the discrepancies in percentages of ON-OFF RGCs measured with the two techniques. One sampling bias is that the multielectrode array appears to undersample pure OFF RGCs, perhaps because the cell bodies of these neurons are further from the electrodes. Thus, in P30 mice, only 2% of all RGCs were found to have pure OFF responses in array recordings. In contrast, the number of OFF RGCs measured by stratification patterns in the YFP-Thy-1 mice was 30%, and previous studies with intracellular recordings found 44% (Stone and Pinto, 1993). This undersampling of OFF RGCs may explain why the percent of ON-OFF cells is greater as measured by the array versus the morphology. Because all measurement techniques have some sampling bias, a strength of this paper is that the observed effects of dark rearing reveal consistent results with two independent techniques.

These results suggest alternative explanations for effects of dark rearing on visual circuits. Ferrets dark reared before eye opening have an increased number of LGN neurons with combined ON and OFF-center receptive fields, which was previously interpreted as a failure of segregation of ON and OFF RGCs inputs onto LGN neurons (Akerman et al., 2002). However, the results from Tian and Copenhagen suggest that this effect could be due to a dark rearing-induced increase in the number of ON-OFF RGCs. This latter interpretation is consistent with the finding that a pharmacological blockade of signaling in the ON pathway in the retina prevents RGC dendritic pruning, which causes an increase in the number of ON-OFF LGN neurons (Bisti et al., 1998). In addition, because ON/OFF properties are important for the synthesis of basic receptive field features in V1, like orientation selectivity, these results suggest that some of the effects of dark rearing on V1 orientation maps (White et al., 2001) may be due to abnormal development in the retina.

The current study focuses on changes of RGC receptive field properties that occur after the onset of light responses. However, the segregation of RGC dendrites starts long before eye opening. Indeed, Tian and Copenhagen found that at P10, 47% of RGCs are stratified into either ON or OFF sublamina. Moreover, by P8 in mouse, before visual responses and even before significant levels of glutamatergic input onto RGCs, some RGC dendrites stratify into ON and OFF sublaminae (Bansal et al., 2000). Further experiments must be done to determine whether initial establishment and maintenance of RGC dendritic stratification are governed by the same

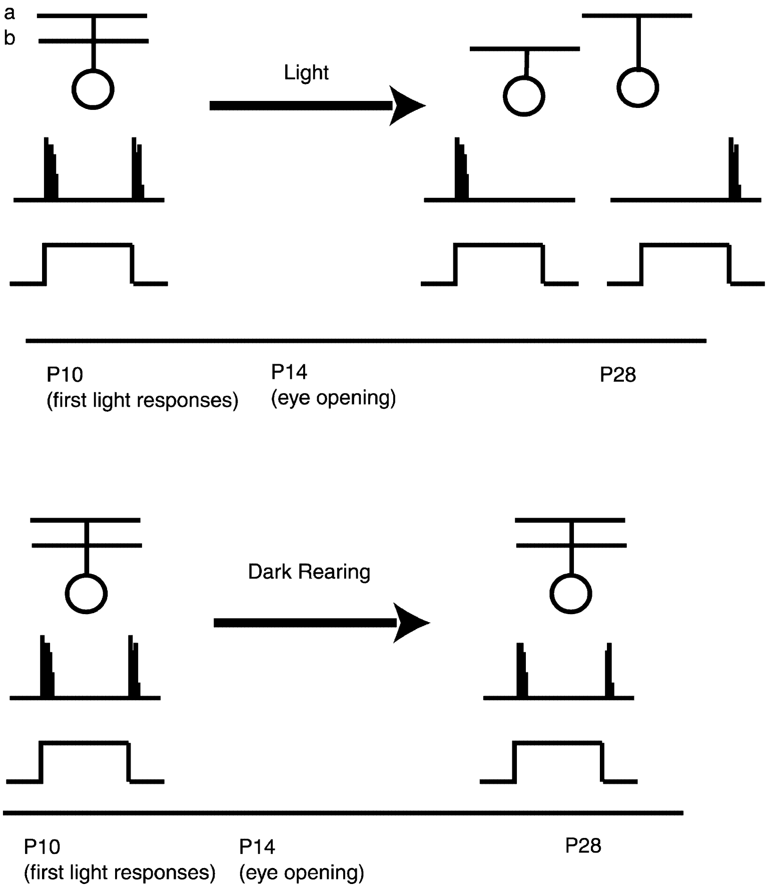

Figure 1. Visual Experience Is Required for Dendrites of Some Retinal Ganglion Cells to Become Stratified into a Single Sublamina in the Innerplexiform Layer

Cells that stratify in sublamina a (OFF sublamina) respond to decreases in illumination. Cells that stratify in sublamina b (ON sublamina) respond to increases in illumination. Cells with dendrites in both sublaminae respond to both increases and decreases in illumination.

mechanisms and whether these mechanisms apply across all classes of RGCs.

How does visual experience drive pruning of RGC dendrites? Dark rearing is not likely to silence RGCs, since it is well established in vitro with multielectrode array recordings that RGCs fire action potentials in the dark (Brivanlou et al., 1998). A recent analysis of spontaneous firing in mouse retina reveals that in the dark, highly correlated firing patterns induced by retinal waves persist until P21, and these spontaneous firing patterns are not altered by dark rearing (Demas et al., 2003). Hence, correlated firing persists during a significant portion of the dark-rearing period used by Tian and Copenhagen. These results argue that highly correlated patterns induced by waves are not sufficient to drive activity-dependent refinement of RGC dendrites. Visual-driven activity, even through closed eyelids (Akerman et al., 2002), must therefore contain uniquely appropriate patterns to drive activity-dependent stratification of RGC dendrites.

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