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Report

Cannabinoid Receptor Blockade Reveals Parallel Plasticity Mechanisms in Different Layers of Mouse Visual Cortex

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SUMMARY

The ocular dominance (OD) shift that occurs in visual cortex after brief monocular deprivation (MD) is a classic model of experience-dependent cortical plasticity. It has been suggested that OD plasticity in layer 2/3 of visual cortex precedes and is necessary for plasticity in the thalamocortical input layer 4. Here, we show in mouse visual cortex that rapid OD plasticity occurs simultaneously in layers 2/3 and 4. Remarkably, pharmacological blockade of cannabinoid receptors completely prevents the OD shift in layer 2/3, leaving plasticity intact in layer 4. Thus, experience-dependent cortical modifications in layers 2/3 and 4 can occur in parallel, via distinct mechanisms. These findings simplify the mechanistic description of plasticity in layer 4, force a revision in the interpretation of previous studies in which laminar differences in OD plasticity mechanisms were unrecognized, and have important implications for the therapeutic use of cannabinoid receptor antagonists in humans.

INTRODUCTION

The loss of visual responsiveness to an eye temporarily deprived of vision has taught us much about how the cerebral cortex is modified by experience during postnatal development. This ocular dominance (OD) shift following monocular deprivation (MD) occurs by synaptic modifications within primary visual (striate) cortex, but how and where have remained controversial. Retinal input is relayed via the lateral geniculate nucleus to primary visual cortex, where it is processed by neurons in different cortical layers. The canonical feed-forward cortical microcircuit comprises thalamic input to layer 4 neurons, layer 4 input to neurons in superficial layers (2/3), and superficial layer input to neurons in the deep layers (5/6) which, in turn, project to extrastriate cortical and subcortical structures. Although an OD shift can occur by modification of excitatory geniculocortical connections, layer 4 plasticity is not required for modification of intracortical connections in the superficial layers. Indeed, the view that prevails today is that the OD shift in layer 2/3 actually precedes and is required for the shift in layer 4 (Hensch, 2005; Thompson, 2000; Trachtenberg et al., 2000). If this notion is correct, it adds complexity to the synaptic mechanism of OD plasticity that has yet to be considered in most theories of cortical plasticity.

In the current study, we investigated laminar differences in the early cortical response to MD in mice. We find that as little as one day of MD produces comparable OD shifts in layers 4 and 2/3 that are caused by depression of deprived-eye responses. Moreover, we discovered that systemic injection of a cannabinoid receptor (CBR) antagonist completely blocked the OD shift in layer 2/3 but had no effect on plasticity in layer 4. These data indicate that OD shifts in layers 4 and 2/3 occur independently and in parallel and are mediated by distinct (cannabinoid-independent and cannabinoid-dependent) mechanisms.

RESULTS

Depression of Deprived-Eye VEPs Causes Rapid OD Shifts

While it has been established previously that a maximal OD shift occurs in juvenile mouse visual cortex after 3–4 days of MD (Frenkel and Bear, 2004; Gordon and Stryker, 1996), it was unknown if shorter periods of MD can also initiate a shift. We reasoned that a temporal dissociation of OD plasticity in different layers would likely be apparent during the early stages of MD before the shift becomes asymptotic. Therefore, we began by exploring in greater detail the shift that occurs in visually evoked potentials (VEPs) with brief MD. Chronically implanted electrodes were positioned in layer 4, the site of the maximum negative-going field potential, and measurements of absolute VEP amplitude were made before and after 1–3 days of MD in awake animals.

As shown in Figures 1A–1C, the raw amplitudes of VEPs elicited by full-field, sinusoidal-grating stimulation of the contralateral (deprived) eye (168 ± 15 μV, n = 11) were significantly smaller than their baseline level (213 ± 13 μV, n = 24) following only 1 day of MD ($p < 0.01$, paired t test). Significantly more deprived-eye depression was apparent in a separate group of animals following 3 days of MD (107 ± 10 μV, n = 13; versus baseline $p < 0.01$; versus post-1day MD $p < 0.01$, paired t test). Meanwhile, the response of the ipsilateral (nondeprived) eye was unaffected by either 1 or 3 days of MD (baseline 100 ± 6 μV, versus post-1 day MD 108 ± 6 μV; $p = 0.87$, versus post-3 day MD 100 ± 13 μV, $p = 0.92$, paired t test). As a result of the deprived-eye depression,

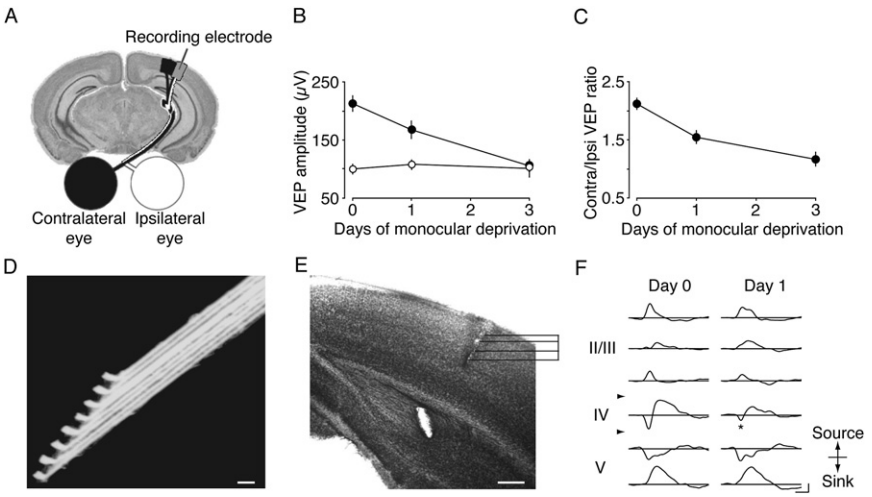

Figure 1. Brief MD Shifts OD in Layer 4 by Deprived-Eye Response Depression

(A) Schematic illustration of the mouse visual pathway and the positioning of VEP recording electrode in layer 4.

(B) Lid suture of the eye contralateral to the recorded hemisphere for 1 and 3 days significantly reduces the amplitude of responses (mean ± SEM) evoked by stimulation of the deprived eye (filled circles) without affecting open-eye responses (open circles; day 0 n = 24; day 1 n = 11; day 3 n = 13).

(C) Shift of the contralateral-to-ipsilateral VEP amplitude ratio following MD.

(D) Photograph of an eight-channel array designed for simultaneous chronic recordings of field potentials and single-unit activity at multiple cortical depths (Scale bar, 100 μm).

(E) A Nissl stained section containing electrolytic lesions (indicated with lines) at various cortical layers from an animal chronically implanted with the multichannel array. The angle of array penetration was adjusted to achieve collection of laminar responses normal to the cortical surface. Scale bar, 200 μm.

(F) CSD profile constructed from field potentials evoked by contralateral (deprived) eye stimulation before and after 1 day MD reveals a robust reduction of the current sink (downward deflections; asterisk) in layer 4 following brief MD. Day 0, baseline; day 1, 1 day post-MD. Scale bar, 50 ms, 0.002 Vmm^{-2}.

the ratio of contralateral to ipsilateral VEP amplitudes, an index of ocular dominance, underwent a quantitative decrease following brief periods of MD (baseline pre-1 day MD 2.1 ± 0.1, post-1 day MD 1.6 ± 0.1; baseline pre-3 day MD 2.2 ± 0.1, post-3 day MD 1.2 ± 0.1; baseline pre-1 day MD versus post-1 day MD, $p = 0.02$; baseline pre-3 day MD versus post-3 day MD, $p < 0.01$; baseline pre-1 day MD versus baseline pre-3 day MD, $p = 0.86$; post-1 day MD versus post-3 day MD, $p = 0.03$; Fisher's PLSD). These data demonstrate that a significant OD shift is induced in mouse visual cortex by as little as 1 day of MD.

Brief MD Depresses the Layer 4 Current Sink Evoked by Deprived-Eye Stimulation

Because of the position of the electrode, the chronic VEP recordings suggest that a rapid OD shift occurs in layer 4. However, VEPs reflect net synaptic currents with contributions potentially from all layers. Thus, the formal possibility remained that the surprisingly rapid OD shift of VEPs observed in layer 4 was actually a reflection of synaptic changes in superficial layers. To better resolve the locus of change, we performed a current source density (CSD) analysis of responses before and after 1 day of MD.

CSD analysis is commonly accomplished by sequential sampling of field potentials from a single electrode tracked along a line normal to the cortical surface. This approach is valid if it can be assumed that the repeated exposure of the animal to visual stimulation does not alter the responses during the course of the experiment. However, recent findings have challenged the validity of this assumption, at least in awake animals. For example, fast recovery from MD has been reported following binocular exposure (Krahe et al., 2005; Mitchell et al., 2001), and a robust form of synaptic potentiation can be induced upon repetitive exposure to grating stimuli in awake mice (Frenkel et al., 2006). We therefore constructed a multichannel array that could be implanted chronically (Figures 1D and 1E), enabling simultaneous collection of field potentials and spiking activity at different depths in the cortex.

The initial CSD profile and the effect of 1 day of MD were consistent across the three animals studied. A representative example is shown in Figure 1F. In all cases, there was an obvious short latency current sink in layer 4 (confirmed histologically) that was depressed after 1 day of MD (post-1day MD, 45.5% ± 6.3% of baseline, $n = 3$, $p = 0.01$, paired t test). This analysis importantly localizes the early deprived-eye response depression to synapses in layer 4.

Brief MD Induces an OD Shift in Neurons of Both Layers 2/3 and 4

The CSD analysis unfortunately did not allow any quantitative comparison of the OD shift in layers 4 and 2/3. The sinks in the superficial layers were difficult to discern, presumably because longer latency events are particularly prone to the canceling effects of currents occurring simultaneously in different layers. However, because units were readily recorded from our multichannel arrays, we were able to perform a classical analysis of OD by measuring relative spiking of neurons in different layers to visual stimulation presented to either eye. We could not be confident that the *same* neurons were recorded from each channel on successive days, but we could take a before- and after-MD sample of visually driven spiking activity in the same layers on successive days. The laminar position of the electrodes was confirmed by histology in every case.

Histograms of spiking relative to stimulus presentation time were generated for each neuron in response to stimulation of each eye. To calculate OD, we subtracted baseline firing from evoked responses and assigned a score based on the difference of the ipsilateral and contralateral (deprived) eye evoked responses divided by the sum of the evoked responses (Rittenhouse et al., 1999). This analysis yields an OD score for each neuron that can range from −1 to +1. Because the responses of neurons to the grating stimulus varied from transient excitation to sustained excitation to transient depression, we used two different approaches to quantify the response. The *peak response* is the maximal deviation from the spontaneous activity, whereas

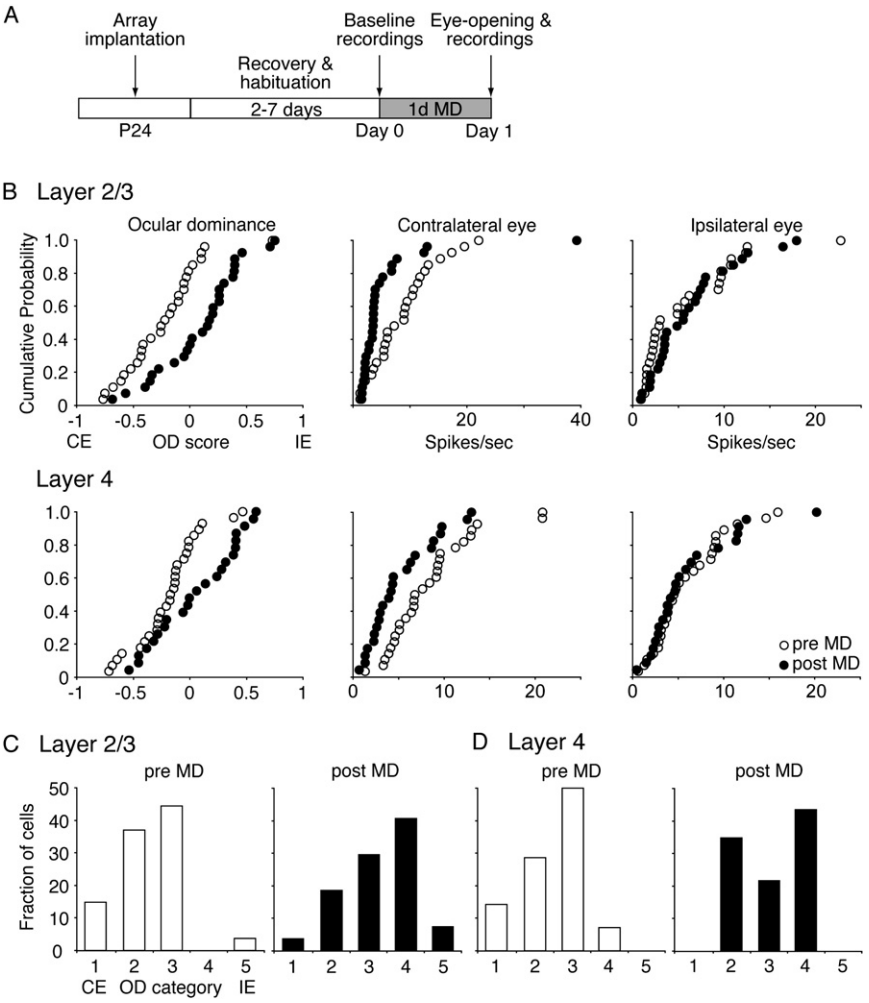

Figure 2. OD Shifts Occur in Single Units in Layers 4 and 2/3 as a Result of 1 Day of Monocular Deprivation

(A) Experimental design.

(B) The distribution of OD scores and evoked firing rates of layer 2/3 (top) and 4 (bottom) neurons is altered by 1 day of MD. Cumulative probability graphs on the left reveal a significant difference between the eye preference of neurons before and after deprivation (CE, contralateral eye; IE, ipsilateral eye; n, number of units from nine animals; n = 27, L 2/3 pre-MD; n = 27, L2/3 post-MD; $p < 0.01$; n = 28, L 4 pre-MD; n = 23, L 4 post-MD; $p = 0.03$, Kolmogorov-Smirnov test). Cumulative probability histograms in the right two columns show changes in the distribution of firing rates before and after MD. Single-unit responses evoked by contralateral (deprived) eye stimulation are significantly shifted leftward as a result of MD in layer 2/3 (top middle, n = 27, pre-MD, open circles; n = 27, post-MD, closed circles; $p < 0.01$; Kolmogorov-Smirnov test), as well as in layer 4 (bottom middle; n = 28, pre-MD, open circles; n = 23, post-MD, closed circles; $p = 0.02$). In contrast, MD has no effect on the response evoked by ipsilateral (nondeprived) eye stimulation in both layers (top right, layer 2/3; $p = 0.33$; bottom right, layer 4; $p > 0.99$).

(C and D) OD histograms before and after MD were constructed by binning the OD values into 5 categories, according to convention.

the *spike deviation* is the sum of all spikes above or below baseline during the entire second of data collection per trial (see Figure S1 available online). Because the choice of measurement did not affect the results, for simplicity we illustrate only the results calculated using peak response.

The baseline recordings revealed, as expected, that most units were dominated by the contralateral eye (OD values <0). However, we observed a significant shift in the OD distribution toward the ipsilateral (nondeprived) eye after 1 day MD. The shift was comparable in the neurons recorded from layer 4 and layer 2/3 (Figure 2). Further analysis of the absolute changes in spiking activity of single units indicated that the OD shift in both layers occurs as a result of the loss of responsiveness to the deprived contralateral eye (Figure 2). Thus, there is no qualitative or quantitative difference in the modification of responses in layers 4 and 2/3 by 1 day of MD, the shortest duration of deprivation that reliably produces an unsaturated OD shift.

Rapid OD Shift in Layer 4 Does Not Require Layer 2/3 Plasticity

Endocannabinoids are retrograde synaptic messengers that are synthesized and released by postsynaptic neurons and can cause both short- and long-term depression of synaptic transmission in the brain by acting at CBRs (Hashimotodani et al., 2007). In the rodent cerebral cortex, cannabinoid receptor expression is highest in layer 2/3 and lowest in layer 4 (Deshmukh et al., 2007; Hill et al., 2007). Consistent with this anatomical distribution, long-term synaptic depression (LTD) is blocked by the CBR inverse agonist AM 251 in layer 2/3 of mouse visual cortex, but not in layer 4 (Crozier et al., 2007). Because AM 251 readily crosses the blood-brain barrier and produces durable inhibition of CBRs (Gatley et al., 1996), we explored whether this drug could selectively interfere with OD plasticity in the superficial layers of visual cortex.

The effects of systemic AM 251 on activity in a cortical network are expected to be complex since it should acutely increase the probability of both GABA and glutamate release by reducing tonic activation of CBRs at synapses where these receptors are expressed. Indeed, we found that acute systemic injection of AM 251 reliably altered VEP waveforms, presumably by shifting the balance of current sinks and sources in the cortex. For our purposes, the biophysical basis for the change in the VEP is less important than the fact that it can be used to monitor the duration of AM 251 action in visual cortex. We found that a single injection of AM 251 (5 mg/kg i.p.) produced significant changes within 30 min that persisted for 12 hr but returned completely to baseline by 24 hr postinjection (Figure S2). Thus, a single systemic injection of AM 251 can interfere with CNS endocannabinoid

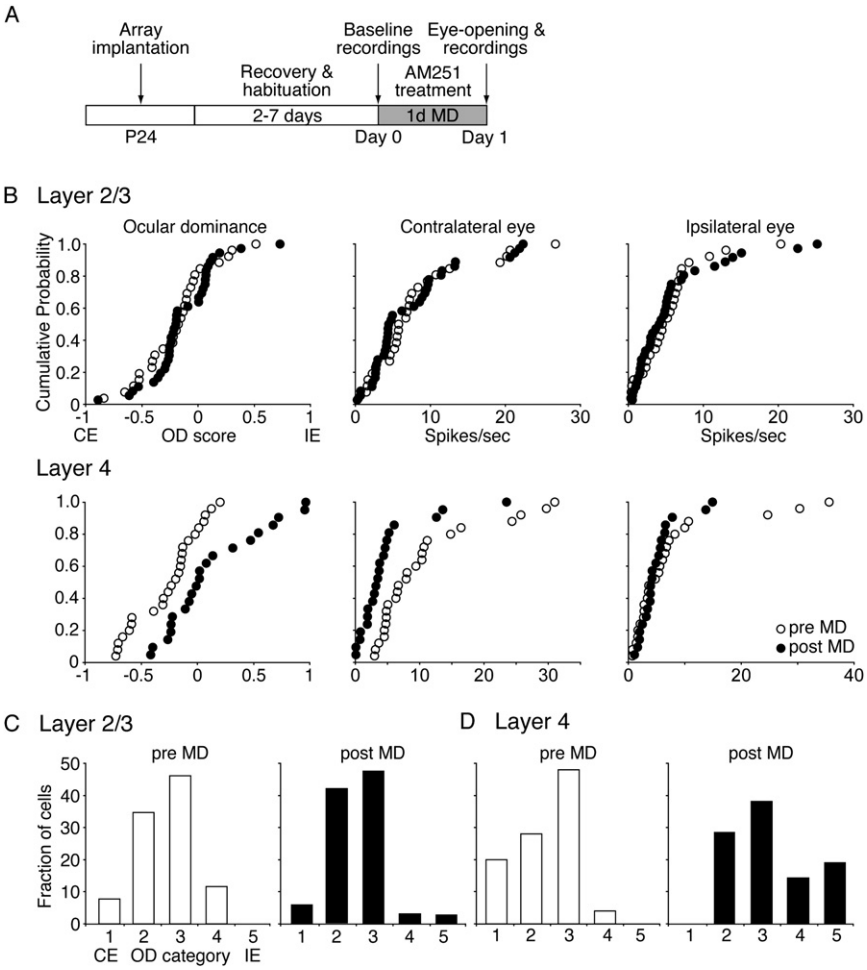

Figure 3. An Antagonist of Cannabinoid Receptors Selectively Prevents the Change Evoked by 1 Day of Monocular Deprivation in Layer 2/3 while Preserving the OD Shift in Layer 4

(A) Experimental design.

(B) Analysis of single-unit response reveals a failure of layer 2/3 neurons to exhibit OD plasticity following AM 251 treatment. Top: The cumulative probability graph of the distribution of OD scores from layer 2/3 neurons (top left) are indistinguishable between pre (n, number of units from 13 animals; n = 26)- and post (n = 36; p = 0.62; Kolmogorov-Smirnov test)-MD conditions. In contrast, a significant OD shift is detected in layer 4 neurons from the same AM 251-injected animals (bottom left, n = 25, pre-MD; n = 21, post-MD; p = 0.03). Similarly, single-unit responses evoked by contralateral (deprived) eye stimulation is comparable before and after MD in layer 2/3 (top middle, n = 26, pre-MD, open circles; n = 36, post-MD, closed circles; p = 0.22, Kolmogorov-Smirnov test) of AM 251-injected animals, while a significant decrease is observed in layer 4 (bottom middle, n = 25, pre-MD, open circles; n = 21, post-MD, closed circles; p < 0.01). No apparent change is found in ipsilateral (nondeprived) eye-evoked responses (top right, layer 2/3; p = 0.81; bottom right, layer 4; p = 0.98).

(C and D) OD histograms before and after MD were constructed by binning the OD values into five categories, according to convention.

signaling for most of the period of MD, without being on board during the measurement of OD plasticity 24 hr later.

Using unit recordings from a chronically implanted electrode array, we examined the effects of 1 day of MD in mice injected with AM 251 immediately after closing the contralateral eyelid (Figure 3). Recordings from neurons in layer 4 revealed a normal OD shift characterized by a robust decrease in responsiveness to the deprived eye. Furthermore, the shift of relative eye preference was indistinguishable from that in uninjected controls (Figure S3). In striking contrast, no OD shift occurred in layer 2/3 after one day of MD in AM 251-treated mice. In terms of both OD scores and absolute firing rates, there was no difference in layer 2/3 neurons after 1 day of MD from the baseline measurements. Therefore, we conclude that OD plasticity in layer 2/3 is uniquely sensitive to CBR blockade and that robust layer 4 plasticity can proceed normally in the absence of layer 2/3 modification.

Although peripheral to the aims of the current study, it is clearly of interest to understand precisely how systemic AM 251 selectively blocks the OD shift in layer 2/3. One simple explanation would be a disruption of visually evoked activity. To examine this possibility, we recorded unit activity before and 1 hr after injection of AM 251 (5 mg/kg i.p.). We observed no significant differences in evoked or spontaneous activity, ocular dominance, or orientation selectivity (Figure 4). Thus, although we cannot rule out more subtle modifications of receptive field properties, the disruption of plasticity in layer 2/3 is likely not due to a gross disturbance in visual responses.

It is of interest to note, however, that the VEPs recorded simultaneously on the same channels as the units showed the expected increase in amplitude. VEPs reflect the summed excitatory synaptic currents, whereas spikes reflect the integrated output of a single neuron. Thus, the drug treatment may alter the input-output function of the visual cortex. It is conceivable that simultaneous increases in synaptic excitation and inhibition cancel at the level of the spiking of individual neurons.

DISCUSSION

The major conclusion of this study is that in mouse visual cortex, layer 2/3 OD plasticity neither precedes nor is necessary for layer 4 plasticity. This finding forces a revision in current dogma and simplifies the mechanistic requirements for layer 4 plasticity—which potentially could be explained simply by "Hebbian" modification of the feed-forward connections from thalamus to cortex, as originally envisioned by Hubel and Wiesel (Wiesel, 1982) and assumed in prominent theories of cortical plasticity (Bienenstock et al., 1982).

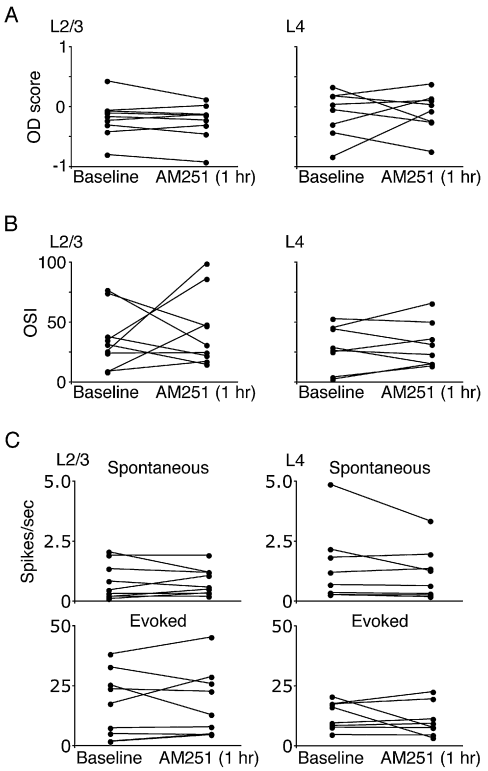

Figure 4. Acute Injection of a Cannabinoid Receptor Antagonist Does Not Grossly Affect the Firing Rates or Stimulus Selectivity of Neurons in Layers 2/3 or 4

(A) OD scores of layer 2/3 (n, number of units from four animals; n = 9; p = 0.31) and layer 4 (n = 8; p = 0.86, paired t test) neurons are not significantly altered by acute AM 251 treatment.

(B) Similarly, no statistically significant difference is found in the OSI of layer 2/3 (n = 9; p = 0.58) and layer 4 (n = 8; p = 0.79, paired t test) neurons following AM 251 treatment.

(C) Neither spontaneous (layer 2/3, p = 0.94; layer 4, p = 0.21) nor contralateral-eye evoked response rate (layer 2/3, p = 0.87; layer 4, p = 0.49; paired t test) was affected by AM 251.

At this point, we can only speculate as to why superficial layer plasticity is blocked by AM 251. An appealing hypothesis is suggested by the finding that LTD in layer 2/3, but not layer 4, is blocked by AM 251 (Crozier et al., 2007). LTD was introduced as an experimental paradigm to study the mechanisms of deprivation-induced synaptic depression in visual cortex (Bear, 2003). Synaptic depression caused by prior MD in vivo occludes LTD in both layers 2/3 and 4 of mouse visual cortex (Crozier et al., 2007). Thus, the evidence suggests that deprivation induces synaptic depression via mechanisms that are revealed by the study of LTD and that these differ in layers 4 and 2/3. AM 251 likely prevents layer 2/3 OD plasticity by blocking this mechanism for deprived-eye depression; thereby isolating the changes caused by endocannabinoid-independent mechanisms in layer 4.

Our findings also challenge the canonical feed-forward cortical microcircuit in mouse visual cortex. If layer 2/3 neurons depend on layer 4 for the majority of their excitatory afferent drive, one would expect that the OD shift observed in layer 4 would be passively reflected in the responses of layer 2/3 neurons. However, there was no hint of an OD shift in layer 2/3 of the AM 251-treated mice despite full expression of the shift in layer 4. In other words, the deprived-eye "channel" was depressed in layer 4 but unaffected in layer 3. This finding suggests that functional deprived-eye input to layer 3 can bypass layer 4. The anatomical substrate of this input remains to be determined, but is likely to be direct LGN projections to layer 2/3, which are substantial in the mouse (Antonini et al., 1999).

Parallel processing of information from retina to LGN to cortex appears to be a general principle of visual system organization in many species. The classic example is the macaque monkey, where parallel processing streams from magno-, parvo-, and koniocellular LGN layers terminate in cortical layers 4Cα, 4Cβ, and 3, respectively. For many years, it has been appreciated that these pathways are modified by deprivation at different rates (see, e.g., LeVay et al., 1980). Our results suggest that plasticity of parallel processing streams can occur by distinct molecular mechanisms.

Finally, we note that CBR antagonists are currently under development for the treatment of obesity in humans (Patel and Pathak, 2007). Our finding of a profound disruption of cortical plasticity in juvenile mice treated with AM 251 suggests caution is advised in the use of such compounds in children.

EXPERIMENTAL PROCEDURES

Subjects

C57Bl/6 mice were used for all experiments. Animals were group housed and kept on a 12 hr light/dark cycle. All animals were treated in accordance with NIH and MIT guidelines.

Drug Preparation and Administration

AM 251 was dissolved in a vehicle solution containing Tween 80 (10%), dimethyl sulfoxide (DMSO, 20%), distilled water (70%) and was administered through intraperitoneal injections (5 mg/kg). Equal volumes of vehicle were injected into control animals. AM 251 was purchased from Tocris. Tween 80 and DMSO were purchased from Sigma.

In Vivo Electrophysiology

VEP recordings (Figure 1) were performed as previously described (Sawtell et al., 2003). Briefly, VEPs were measured in binocular visual cortex using tungsten microelectrodes (FHC) inserted in the middle of the cortical thickness in awake, head-restrained mice. VEPs were elicited using full-field, sine-wave gratings (0.05 cycle/degree, 100% contrast) with a fixed temporal frequency (1 Hz). For CSD analysis and single-unit recordings, a custom-made multichannel linear array (Figure 1D) consisting of eight tungsten microwires (California Fine Wire) attached by instant adhesive (Small Parts, Inc.) were implanted and fixed in place with dental acrylic. Field potentials and spike activity evoked by sinusoidal gratings or by a blank screen with equal luminance in awake, head-restrained mice were collected using commercially available hardware and software. Output from each recording electrode was split, directed to preamplifiers, bandpassed filtered for spikes (300–3000 Hz) and for local field potentials (1–300 Hz), and sent to a PC running the data acquisition software. CSD profiles were approximated by the second spatial derivative of field potentials (Mitzdorf, 1985) collected on channels immediately adjacent to each other (differentiation grid = 1) by the equation $[d(n) \cdot (Vn+1 - Vn) - d(n') \cdot (Vn - Vn-1)]/0.5 \cdot d(n) \cdot d(n') \cdot [d(n) + d(n')]$, where Vn−1, Vn, and Vn+1 stand for the field potentials recorded at electrode n−1, n, and n+1, and d(n) is the distance between electrode n−1 and n, and d(n′) is the distance between electrode n and n+1.

For recorded spikes, offline discrimination of single unit activity was based on waveform shape while multiunit activity was excluded. Spike trains were

smoothed by convolution with a Gaussian kernel (sigma = 100 ms). The results of differencing between grating-evoked versus blank screen spike activity (Figure S1) when stimuli were presented to the contralateral (CE) and ipsilateral (IE) eye were utilized to calculate the OD score, defined as (IE − CE)/(IE + CE) (Rittenhouse et al., 1999). Previous work has established that repeated stimulus presentations induce plasticity in awake mice (Frenkel et al., 2006). Therefore, as for the VEP recordings, we used one cardinal orientation (0° or 90°) for collecting baseline unit responses and the orthogonal orientation for collecting unit responses after MD. This procedure is possible because the large majority of units in mouse visual cortex respond to the cardinal orientations. To optimize the stimuli for each unit would have induced plasticity that would confound our measurements of OD plasticity.

In experiments designed to assess acute effects of AM 251, analysis of the orientation selectivity index (OSI) was adopted from the methods previously described (Chapman and Stryker, 1993; Worgotter and Eysel, 1987). Since phase-reversing gratings were used to evoke the response, the amplitude of the first harmonic component following Fourier transform of the orientation tuning curve was chosen for OSI estimation.

At the end of experimentation, lesions were introduced at selected channels on the array or VEP recording electrodes (8 μA, 6–8 s), and brains were removed for histological validation of recording sites.

SUPPLEMENTAL DATA

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/58/3/340/DC1/.

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