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Synapse Rearrangement

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CHAPTER 8

Molecular substrates of plasticity in the developing visual cortex

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Abstract: Ocular dominance plasticity may be the paradigmatic in vivo model of activity-dependent plasticity. More than four decades of intense research has delineated the network-level rules that govern synaptic change in this model. The recent characterization of a murine model for ocular dominance plasticity has facilitated rapid progress on a new front, extending our understanding of the molecular mechanisms underlying ocular dominance plasticity. In this review, we highlight recent advances in this research effort, focusing in particular on signaling pathways mediating shifts in ocular dominance, and mechanisms underlying the timing of the critical period.

Keywords: plasticity; cortex; mouse; ocular dominance; critical period; monocular deprivation

Introduction

The brain harbors an extraordinary number of connections in a singularly small volume — by one estimate, 300×10^6 synapses per square millimeter of neocortex (Beaulieu and Colonnier, 1983). In no small part, this welter of connectivity is achieved through activity-driven rearrangements of neural circuits. The rules which govern this activity-dependent plasticity are perhaps best understood in the mammalian visual cortex, where plasticity induced by monocular deprivation — ocular dominance plasticity — has been studied for decades and is relatively well characterized.

In many carnivorous species (including cats, which comprise the most-studied and best-characterized animal model of ocular dominance plasticity), thalamocortical afferents representing the two eyes arise in the lateral geniculate nucleus (LGN) of the thalamus, and converge on layer IV of the primary

visual cortex (V1), providing the first anatomical substrate for binocular interactions. In seminal experiments, David Hubel and Torsten Wiesel showed that these neural circuits could be profoundly shaped by manipulations of an animal's visual environment. Brief closure of one eye resulted in dramatic rearrangements of the connections subserving both the deprived and the nondeprived eyes, with the cortical territory devoted to the former shrinking, and those devoted to the latter expanding (Wiesel and Hubel, 1963).

Experiments elaborating on these initial observations have painted a remarkably clear picture of the rules governing activity dependent competition in ocular dominance plasticity. Importantly, activity-dependent change in the cortex is competitive, pitting afferents representing the two eyes against one another in a battle for cortical territory. Synaptic change in ocular dominance plasticity is Hebbian: effective, depolarizing inputs drive stronger synaptic connections, while ineffectual inputs are weakened. In addition, these competitive interactions are largely confined to a developmental critical period, a

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97 temporally circumscribed window in which synapses
98 are exceptionally plastic.

99 The successes of carnivore models in elucidating
100 the rules of ocular dominance plasticity have been
101 complemented in recent years by the characterization
102 of a mouse model for ocular dominance plasticity.
103 Unlike larger mammals such as primates and cats, the
104 mouse has been the subject of intense genetic analysis
105 and manipulation. Technologies which enable the
106 stable introduction of genes into the mouse genome,
107 yielding transgenic mice, coupled with complemen-
108 tary protocols which enable discreet DNA sequences
109 to be removed from the genome, producing knock-
110 out (KO) mice, have added an immensely valuable
111 tool to the arsenal of pharmacological, electrophys-
112 iological, and anatomical methods which have
113 traditionally been used to study ocular dominance
114 plasticity. As a consequence, our knowledge of the
115 molecular processes that govern plasticity is growing
116 rapidly.

117 Insights gleaned from studies of mutant mice have
118 not been confined to the molecular mechanisms
119 underlying ocular dominance plasticity. Studies of
120 transgenic animals have also generated new under-
121 standing of an old question, by shedding light on how
122 the timing of the critical period is controlled.

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124

125 **Murine model of ocular dominance plasticity**

126

127 Ocular dominance plasticity in mice is robust (the
128 magnitude of plasticity following monocular depriva-
129 tion in mice is roughly 85% as large as that seen in
130 cats), rapid (with four days required for near-satu-
131 rating shifts in mice, and two for cats), and regular
132 (ocular dominance plasticity in mice is governed by
133 the same rules which have been identified in
134 carnivores, as detailed further in the chapter).

135 Key studies by [Gordon and Stryker \(1996\)](#) have
136 demonstrated that ocular dominance plasticity is
137 subject to the same rules first elucidated in higher
138 mammals. Deprivation results in a competition-
139 driven rearrangement of connections subserving the
140 two eyes — while monocular deprivation drives
141 robust plasticity, binocular deprivation has little if
142 any consequence, ruling out simple disuse effects. The
143 effects of monocular deprivation are maximal in mice
144 when deprivation is initiated in a well-defined critical

period, which peaks near postnatal day 26. Similar
deprivations initiated in adulthood have little effect.

As for higher mammals, monocular deprivation in
mice results in both physiological and anatomical
changes. The latter are most pronounced in the
afferents subserving the ipsilateral projections of the
deprived eye, which are much reduced (as revealed by
transneuronal labeling) after prolonged deprivation
([Antonini et al., 1999](#)).

Signaling pathways

The molecular pathways that underlie ocular
dominance plasticity parallel the themes that emerge
from other well-studied forms of neuronal plasticity,
such as long-term potentiation (LTP). The N-methyl-
D-aspartate (NMDA) receptor is critical, and likely
initiates a number of second-messenger mediated
signaling pathways by allowing influx of Ca^{2+} after
glutamate binding and release of Mg^{2+} blockade,
which has been demonstrated in vitro. Downstream
signaling likely proceeds through activation of the
molecule cyclic AMP response element binding
protein (CREB), which initiates transcriptional
changes, and subsequent translational events. Trans-
lational events are likely to facilitate the anatomical
changes induced by monocular deprivation. A small
but growing number of molecules have been
identified which may contribute to these structural
changes, which must include processes underlying
both proliferation and growth of connections
subserving the nondeprived eye, and pruning and
retraction of the connections from the deprived eye.

NMDA receptor

Characterization of the NMDA receptor's properties
in vitro suggested that the molecule might play a
central role in ocular dominance plasticity, acting as
the lynchpin for Hebbian plasticity by serving as the
“coincidence detector” of convergent depolarizing
input. Despite the attentions of a number of
investigators, solid evidence of a role for the
NMDA receptor in ocular dominance plasticity,
apart from a simple role in basal synaptic transmis-
sion, was difficult to establish. Numerous pharma-
cological experiments showed that blockade of the

145 NMDA receptor prevents ocular dominance plasticity (Kleinschmidt et al., 1987; Gu et al., 1989; 146 Bear et al., 1990), but such manipulations have 147 potent suppressive effects upon normal synaptic 148 transmission (Miller et al., 1989). A technically 149 innovative solution to this problem came in the form 150 of infusion of anti-sense DNA directed against the 151 NR1 subunit of the NMDA receptor, a manipulation 152 which substantially and selectively suppressed 153 NMDA receptor transmission, without affecting 154 visually driven responses in the visual cortex 155 (Roberts et al., 1998). This manipulation also blocks 156 the effects of monocular deprivation, suggesting that 157 once the NMDA receptor's putative correlation 158 detection role is carefully dissected from its role in 159 normal synaptic transmission, the former indeed 160 exists, and is necessary for ocular dominance 161 plasticity. 162

163 164 *Metabotropic glutamate receptor (mGluR)*

165
166 There is little direct evidence for a role of the mGluRs 167 in ocular dominance plasticity, though they are 168 required for various forms of plasticity in vitro 169 (Balschun et al., 1999). Blockade of mGluR function 170 with the antagonist (*RS*)-alpha-methyl-4-carboxy- 171 phenylglycine (MCPG) has no effect upon ocular 172 dominance plasticity (Hensch and Stryker, 1996); the 173 latter finding has been challenged on the grounds that 174 MCPG does not adequately block the effects of 175 mGluR action in the visual cortex (Huber et al., 176 1998). However, further investigation of a role for 177 mGluRs, using a mutant mouse lacking mGluR2, has 178 demonstrated that these mice possess normal visual 179 cortical plasticity when subjected to monocular 180 deprivation (Renger et al., 2002). To date, mGluR2 181 is the sole receptor subtype that has been tested for 182 a role in ocular dominance plasticity. 183

184 185 *Neurotrophins*

186
187 The properties of neurotrophin molecules — their 188 promotion of axonal growth and dendritic prolifera- 189 tion (McAllister et al., 1995, 1996), activity dependent 190 release (Blochl and Thoenen, 1995), and presence in 191 the visual cortex and regulation by activity there 192 (Castren et al., 1992) — make them compelling

targets for investigation of a potential role in ocular 193 dominance plasticity. Indeed, a great number of 194 studies have attempted to elaborate a role for these 195 molecules in mediating ocular dominance shifts 196 following monocular deprivation, and to substantiate 197 a “neurotrophic hypothesis for ocular dominance 198 plasticity” — the attractive notion that thalamocor- 199 tical afferents might engage in activity-driven 200 competition for neurotrophins, which would in turn 201 promote axonal growth and the formation of new 202 synapses (Berardi et al., 2003). While the precise role 203 of neurotrophin signaling in ocular dominance 204 plasticity is unknown, investigators of the visual 205 system have amassed a substantial amount of data 206 that is consistent with this hypothesis.

207 208 *Nerve growth factor (NGF)*

209
210 Early studies in the rat demonstrated that 211 intraventricular infusion of NGF could prevent shifts 212 in ocular dominance following monocular depriva- 213 tion (Domenici et al., 1991). Subsequent studies 214 confirmed this effect and extended it, demonstrating 215 that intracortical infusion resulted in a similar 216 blockade of ocular dominance plasticity, without 217 detectable effects upon levels of neural activity 218 (Domenici et al., 1992; Lodovichi et al., 2000). 219 Moreover, infusion of antibodies that specifi- 220 cally activate the NGF receptor *trkA* prevents the 221 shift in ocular dominance responses that normally 222 follow monocular deprivation (Pizzorusso et al., 223 1999).

224
225 In contrast to the robust effects seen in the rat, 226 infusion of exogenous NGF in the cat has little or no 227 effect. Intraventricular infusion of NGF attenuates 228 ocular dominance plasticity and its behavioral 229 consequences (Carmignoto et al., 1993; Fiorentini et 230 al., 1995), but direct cortical infusion leaves plasticity 231 intact (Galuske et al., 2000; Gillespie et al., 2000; 232 Silver et al., 2001). It is not clear what accounts 233 for this species difference. Silver et al. (2001) have 234 noted that in the rat, unlike the cat, cholinergic 235 afferents to the cortex have focal arborizations, which 236 could allow local infusions of NGF to have relatively 237 more profound effects on the activity of these 238 neurons, which would in turn drive greater cortical 239 activity.

193 *Brain derived neurotrophic factor (BDNF)*

194

195 Intracortical infusion of BDNF partially blocks the
196 effects of monocular deprivation in the rat, but also
197 has significant effects upon spontaneous and evoked
198 neural firing rates, decreasing the signal to noise ratio
199 in cortical neurons (Lodovichi et al., 2000). For this
200 reason, BDNF effects on plasticity should be
201 interpreted with caution, as they may be consequent
202 to changes in cortical activity. Experiments in which
203 BDNF was infused into cat visual cortex (area 18)
204 support this notion, as this manipulation paradoxically
205 results in the expansion of connections
206 subserving the deprived eye (Galuske et al., 2000).
207 It has previously been shown that intracortical
208 infusion of the GABA_A agonist muscimol, which
209 silences cortical neurons, causes a similar reverse
210 plasticity effect (Reiter et al., 1986). Though the
211 activity-suppressing effects of BDNF infusions make
212 the precise role of the molecule in ocular dominance
213 plasticity difficult to interpret, anatomical studies
214 suggest that BDNF has potent growth-promoting
215 effects in primary visual cortex. For instance, BDNF
216 infusion into kitten V1 desegregates ocular dominance
217 columns in normal and deprived kittens (Hata
218 et al., 2000).

219 Recent studies of a mutant mouse heterozygous
220 for the null allele of BDNF (homozygous mutants die
221 prior to the onset of the critical period) demonstrate
222 that a 50% reduction in the protein product of the
223 BDNF gene has no effects upon ocular dominance
224 plasticity (Bartoletti et al., 2002).

225 Studies of mutant mice overexpressing BDNF in
226 the cortex have revealed a critical role for the
227 molecule in regulating the timing of the critical period
228 (see "Timing of the critical period"). This may be
229 distinct from any role the molecule might play in
230 mediating the competition between deprived and
231 nondeprived eye arbors.

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235 *Neurotrophin 3 (NT-3)*

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237 Neither intracortical infusions of NT-3 into the rat
238 (Lodovichi et al., 2000) or the cat (Gillespie et al.,
239 2000) have discernable effects upon ocular dominance
240 plasticity.

Neurotrophin 4 (NT-4)

Like BDNF, intracortical infusion of the trkB ligand
NT-4 has potent effects upon ocular dominance
plasticity, blocking monocular deprivation-induced
changes in both the rat (Lodovichi et al., 2000) and
the cat (Gillespie et al., 2000). However, the latter
study found that infusion of the NT-4 made cortical
neurons generally less responsive, and so caution in
interpreting these results is warranted. On the other
hand, it is abundantly clear that the effects of NT-4
are not the trivial consequence of changes in neuronal
responsiveness. NT-4 infusion degrades orientation
selectivity, reverses a pre-existing shift in ocular
dominance (Gillespie et al., 2000), and causes
anatomical desegregation of ocular dominance
columns (Cabelli et al., 1995, 1997), results that are
all consistent with growth-promoting effects that
have been documented in vitro (McAllister et al.,
1995).

Protein kinase A (PKA)

Using pharmacological approaches, the second
messenger effector PKA has been implicated in
ocular dominance plasticity. Inhibition of PKA in
kitten V1 blocks plasticity, with minor effects on
neuronal responses (Beaver et al., 2001). Though
mice genetically deficient in the PKA R1 β subunit are
impaired in measures of plasticity in vitro, they show
normal shifts in ocular dominance following
monocular deprivation (Hensch et al., 1998a). It is
known that developmental compensation in this
mouse leads to upregulation of the PKA R1 β ~~subunit~~ ^{α} ,
and this may allow plasticity to proceed.

Alpha calcium-calmodulin kinase II (α CaMKII)

α CaMKII is an abundant protein, comprising
between 1 and 2%; of the total protein in the
forebrain (Bennet et al., 1983). Eight to twelve
subunits of the molecule assemble into a rosette
holoenzyme comprised of α and β subunits (in the
forebrain the ratio of α to β subunits is roughly 3 to 1:
Miller and Kennedy, 1985). Once activated by Ca²⁺/
calmodulin binding, α CaMKII can phosphorylate

241 numerous substrate molecules, including the NMDA
242 receptor (Om Kumar et al., 1996) and the transcrip-
243 tion factor CREB (Dash et al., 1991). Importantly,
244 α CaMKII can autophosphorylate at threonine 286.
245 Autophosphorylation switches the molecule into a
246 Ca^{2+} -autonomous state, which allows the molecule to
247 sustain Ca^{2+} -independent kinase activity, in effect
248 providing a mechanism to turn transient Ca^{2+} influx
249 into a sustained plasticity induction signal.

250 α CaMKII is a central player in inducing numerous
251 forms of synaptic plasticity, and ocular dominance
252 plasticity is no exception. Knock-out mice lacking
253 α CaMKII are impaired in ocular dominance plastic-
254 ity (Gordon et al., 1996). Puzzlingly, this deficit was
255 evident in only half of the mutant animals studied,
256 and may be the consequence of compensatory
257 upregulation of other isoforms of α CaMKII (A.
258 Silva, personal communication).

259 More recent studies have confirmed a necessary
260 role for the molecule in ocular dominance plasticity
261 and further shown a specific requirement for
262 α CaMKII autophosphorylation (Taha et al., 2002).
263 Monocular deprivation of mutant mice carrying a
264 single point-mutation — substitution of alanine for
265 threonine 286, which renders α CaMKII unable to
266 autophosphorylate — is ineffective in driving an
267 ocular dominance shift. These mice show neither
268 changes in neuronal responses nor changes in
269 receptive field organization.

270 While confirming the importance of α CaMKII in
271 ocular dominance, these results also clarify the issue
272 of exactly where synaptic change that underlies
273 ocular dominance plasticity occurs. On the basis of
274 pharmacological experiments, some investigators
275 have argued that MD-induced plasticity creates
276 changes primarily in inhibitory synapses (Mower
277 and Christen, 1989). α CaMKII, however, has a
278 precise synaptic distribution, occurring specifically in
279 excitatory neurons, and where localized to synapses,
280 is found postsynaptically only in the postsynaptic
281 density of asymmetric (presumed) excitatory
282 synapses (Liu and Jones, 1996). This specificity,
283 combined with the demonstration of a require-
284 ment for normal α CaMKII function in ocular domi-
285 nance plasticity, suggests that synaptic changes
286 induced by monocular deprivation occur primarily
287 in excitatory synapses made onto glutamatergic
288 neurons.

Extracellular signal-regulated kinase 1,2 (ERK)

ERK (also called mitogen-activated kinase) is
potently regulated both by neural activity and
neurotrophins, and recent experiments in rats have
demonstrated that ERK signaling is required for
ocular dominance plasticity (Di Cristo et al., 2001).
Infusion of an ERK inhibitor directly into the visual
cortex blocks the effects of monocular deprivation,
with little or no effect on neuronal spiking, as well as
blocking LTP in cortical layer II/III (Di Cristo et al.,
2001).

While ERK is known to be activated by increases
in intracellular Ca^{2+} , and therefore may be activated
downstream of NMDA receptor activation, addi-
tional work from the Maffei lab has demonstrated
that neurotrophin signaling can be Ca^{2+} -independ-
ent, and mediated by activation of the ERK
pathway (Pizzorusso et al., 2000). This raises the
tantalizing possibility that the requirement for ERK
in ocular dominance could be downstream of
neurotrophin signaling, a supposition which remains
to be tested.

CREB

PKA, ERK, and α CaMKII signaling ultimately
contribute to changes in nuclear events, likely
converging upon CREB-mediated transcription.
CREB has been implicated in mediating synaptic
plasticity in evolutionarily divergent animals
(*Aplysia*: Dash et al., 1990; *Drosophila*: Yin et al.,
1994; mice: Pham et al., 1999) and widely divergent
plasticity paradigms (late phase hippocampal LTP:
Silva et al., 1998; courtship conditioning in
Drosophila: Griffith et al., 1993; activity-dependent
development in V1: Pham et al., 2001). In a number
of plasticity paradigms, the requirement for CREB
activity seems to be confined to late phases of
plasticity, which has prompted the suggestion that
CREB activity is the molecular bridge linking short-
term changes to long-lasting plasticity (Pittenger and
Kandel, 1998).

In the developing visual system of the mouse,
CRE-mediated transcription is upregulated by
monocular deprivation specifically during the critical
period for ocular dominance plasticity (Pham et al.,

289 1999). This upregulation occurs contralateral to the
290 nondeprived eye, and is not found in binocularly
291 deprived or nondeprived animals. This finding is
292 interesting for two reasons: it shows that CRE-
293 mediated transcription can be driven specifically by a
294 pattern of neural activity which leads to competition
295 — only an imbalance in activity is sufficient to induce
296 it — and that this linkage between activity and
297 transcription is present only during the time of the
298 critical period.

299 CREB is required for ocular dominance plasticity.
300 Using the vaccinia virus to drive expression of a
301 dominant negative form of the molecule in V1,
302 Mower et al. (2002) have shown that blockade of
303 CREB function prevents ocular dominance plasticity.
304 By recording single units at cortical sites both near to
305 and far from the viral injection, the authors
306 demonstrate that plasticity is blocked only in the
307 region in which successful expression of the transgene
308 occurs. Moreover, the effect is reversible. Monocular
309 deprivation starting one week after viral infection, by
310 which time transgene expression had largely
311 dissipated, induced robust ocular dominance shifts.

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315 Structural changes

316 Ultimately, intracellular communication through
317 signaling pathways yields changes in the nuts and
318 bolts of synaptic architecture — for many forms of
319 plasticity, including ocular dominance plasticity,
320 structural changes in synaptic connectivity are the
321 endstage of mechanisms underlying long-lasting
322 change (Antonini and Stryker, 1993, 1996; Antonini
323 et al., 1999). Our understanding of the processes and
324 molecules that underlie these changes is limited, but a
325 handful of promising candidates have been identified.

326

327

328 Protein synthesis

329

330 In many systems, synaptic plasticity is composed of
331 two distinct stages — an early, rapid, and labile stage,
332 followed by a slower, more enduring phase, which is
333 characterized by a requirement for protein synthesis.
334 This requirement for protein synthesis is thought to
335 provide the molecular substrate for structural
336 rearrangements at the synapse, and studies in systems
that provide accessible anatomical preparations, such

as *Aplysia*, bear out this point of view (Bailey and
Chen, 1989; Bailey et al., 1992).

Following monocular deprivation in the mouse,
even the earliest apparent plasticity, as measured
electrophysiologically, requires protein synthesis
(Taha and Stryker, 2002). This requirement for
protein synthesis is confined to the cortex: while
infusion of protein synthesis blockers into primary
visual cortex prevents plasticity following monocular
deprivation, infusion into the LGN has no effect on
plasticity, though infusions at both sites clearly
reduce protein synthesis (to <50% of baseline
levels).

The timing and locus of the requirement for
protein synthesis suggest both that structural
rearrangements occur very rapidly following monoc-
ular deprivation, and that these changes consist
primarily of cortical remodeling, rather than changes
in thalamocortical inputs. This model of rapid
cortical change is supported by demonstrations
that, in the cat, the earliest changes following
monocular deprivation occur outside thalamorecipient
layer IV (Trachtenberg et al., 2000).

Tissue plasminogen activator (tPA)

Tissue plasminogen activator is a serine protease that
has been implicated in remodeling of cellular
processes in many contexts, including neurite out-
growth and cell migration. Mice lacking the gene
encoding tPA show a specific deficit in the late phase
of LTP, which requires transcription and translation,
suggesting a role for the molecule in the structural
remodeling which may underlie the maintenance of
long-lasting synaptic change (Huang et al., 1996).
Measures of tPA activity in organotypic slice cultures
of visual cortex show that activity of the molecule is
tightly coupled to electrical activity (Muller and
Griesinger, 1998). Moreover, proteolytic activity in
vivo is driven by an imbalance in afferent activity.
Mice subjected to monocular deprivation show
significant elevation of tPA activity in the visual
cortex after even a single day of deprivation (Mataga
et al., 2002).

In both mice (Mataga et al., 2002) and cats
(Mataga et al., 1996; Muller and Griesinger, 1998),
tPA is required for normal ocular dominance

337 plasticity. The nature of this requirement appears to
338 differ in the two species. In cats, infusion of a tPA
339 inhibitor into V1 has no effect upon plasticity
340 produced by an initial period of monocular depriva-
341 tion, but blocks the effects of a subsequent reverse
342 occlusion, both physiologically and anatomically. In
343 mutant mice lacking tPA, plasticity induced by
344 monocular deprivation itself is absent. This deficit
345 can be rescued by intraventricular injection of
346 recombinant tPA.

347 ~~Hensch~~ ^{Mataga} et al. (2000) ¹ propose that these divergent
348 findings may have their roots in differences in the
349 connectivity of the visual system of cats and mice,
350 rather than differences in the mechanisms underlying
351 plasticity. In normal mouse V1, the balance of
352 afferent input is tipped heavily in favor of the
353 contralateral eye. Plasticity induced by monocular
354 deprivation of the contralateral eye is therefore likely
355 to primarily reflect underlying growth and prolifera-
356 tion of the open ipsilateral eye. Cats, in contrast, have
357 relatively balanced ipsilateral and contralateral eye
358 input in normal V1. Consequently, loss of deprived
359 eye input may contribute relatively more to the
360 plasticity seen after monocular deprivation.
361 Subsequent plasticity induced by reverse occlusion
362 is likely the consequence of underlying synaptic
363 strengthening processes.

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365

366 *Other candidate structural proteins*

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368 As yet, relatively few molecules have been identified
369 which are known to be directly involved in mediating
370 changes in axonal and synaptic architecture in ocular
371 dominance plasticity. A number of promising
372 candidates have been identified, however. Two of
373 these include the class I major histocompatibility
374 complex (MHC) antigen and candidate plasticity
375 gene 15 (CPG15), both of which were identified in
376 screens targeting genes with activity-driven changes
377 in gene expression (Nedivi et al., 1993; Huh et al.,
378 2000).

379 To date, neither molecules' role in ocular
380 dominance plasticity has been tested, but studies in
381 other experimental systems suggest that they con-
382 tribute to structural changes in neural connectivity in
383 the visual system. CPG15 expression in *Xenopus*
384 *laevis* optic tectum promotes the growth of both

retinotectal presynaptic afferents and postsynaptic
tectal dendrites (Nedivi et al., 1998; Cantalops et al.,
2000). The class I MHC has been implicated in
another experimental paradigm, as mutant mice
deficient in class I MHC-mediated signaling show
abnormal anatomical refinement of retinogeniculate
connections (Huh et al., 2000).

Timing of the critical period

Advances in understanding the mechanisms under-
lying ocular dominance plasticity have accumulated
rapidly, offering the promise of a complete under-
standing of the molecular events linking neural
activity to anatomical change. But outstanding issues
in understanding activity-dependent plasticity in V1
are not confined to elucidating the mechanisms that
underlie strengthening and weakening of neural
connections. The issue of how plasticity in V1 is
controlled temporally is of considerable interest as
well, and until very recently, little was known about
the mechanisms underlying this process. The con-
vergence of studies of neurotrophin action in the
cortex, and of inhibitory circuits in controlling
plasticity, has dramatically increased our under-
standing of the molecular processes that control the
timing of critical period.

Cortical inhibition and timing of the critical period

In an initial study, Hensch and colleagues (Hensch
et al., 1998b) demonstrated that mice deficient in
inhibitory neurotransmission (KO mice lacking the
67-kD isoform of glutamic acid decarboxylase, or
GAD) were impaired in ocular dominance plasticity.
Microdialysis and electrophysiological studies
showed hyperexcitability of the cortical network,
manifested as prolonged V1 neural discharge follow-
ing visual stimulation. A four day period of
monocular deprivation, sufficient to drive near-
saturating plasticity in wild-type mice, had no effect
in GAD KO mice. More prolonged periods of
deprivation resulted in a small, but significant, shift in
responses toward the nondeprived eye. Intracortical
infusion of the benzodiazepine agonist diazepam
rescued plasticity, showing the locus of the deficit

385 was cortical, and establishing a powerful tool for
386 probing the timing of the critical period in these mice.

387 A follow-up study revealed, remarkably, that
388 diazepam rescue of GAD KO mice was not confined
389 to the normal murine critical period for ocular
390 dominance plasticity (Fagiolini and Hensch, 2000).
391 Monocular deprivation concurrent with diazepam
392 treatment in adult GAD KO mice resulted in robust
393 plasticity; plasticity could also be driven in adult
394 GAD KOs without diazepam by prolonging the
395 length of the monocular deprivation. Subsequent
396 experiments revealed that diazepam treatment could
397 drive plasticity in WT mice prior to the normal
398 critical period, but not after it. These findings led the
399 authors to propose that the onset of the critical
400 period was gated by a threshold level of intracortical
401 inhibition, with the mechanism for initiation of the
402 critical period tightly coupled to that underlying its
403 closure. This model received powerful support in the
404 form of a two part experiment: in GAD KO mice,
405 diazepam was infused over the course of the normal
406 critical period (postnatal days 23–33), but prolonged
407 monocular deprivation was not performed until
408 adulthood (postnatal days 45–60). Plasticity was
409 absent in these mice — early diazepam treatment
410 occluded subsequent plasticity in response to
411 prolonged monocular deprivation. These results
412 suggest a threshold level of inhibition to open a
413 transient period of susceptibility to experience-
414 dependent plasticity.

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418 ***BDNF and the development of cortical inhibition***

419

420 Spurred by in vitro studies suggesting a role for
421 neurotrophins in regulating the development of
422 cortical inhibition, Huang and colleagues engineered
423 a transgenic mouse overexpressing BDNF in cortical
424 pyramidal neurons (Huang et al., 1999).
425 Overexpression of BDNF in these mice accelerated
426 the maturation of inhibitory circuits in the cortex
427 as demonstrated by a number of criteria: GAD
428 expression was elevated at young ages, as were
429 parvalbumin-positive inhibitory interneurons, and
430 inhibitory potentials recorded in cortical slices
431 prepared from these mice were larger than those
432 found in wild-type mice.

Precocious development of inhibitory circuits in these mice altered V1 plasticity in a manner that echoed the findings of Hensch and colleagues. Early monocular deprivation, initiated at postnatal day 21 (and assessed using visually evoked potentials), suggested a trend toward increased plasticity in BDNF overexpressing mice relative to wild-types, though this effect was not significant. Monocular deprivation initiated at older ages (p23 and p28) showed significant differences between wild-types and transgenics, but with effects moving in the opposite direction — significant plasticity occurred in wild-types but not transgenics. These results suggested that BDNF expression accelerated the closure of the critical period.

Single unit-studies of the same mice clarified these findings, by demonstrating that plasticity in the transgenics was precocious, both beginning and ending earlier than in wild-type littermates (Hanover et al., 1999).

Together with the studies of the GAD KO mouse, these results provide compelling evidence that BDNF promotes maturation of cortical inhibitory circuits, which in turn gate the critical period for ocular dominance plasticity. These results suggest cortical development of these circuits is central in initiating experience-dependent plasticity, and raises interesting questions about the laminar and functional classes of interneurons involved.

Other candidate timing mechanisms

Pizzorusso et al. (2002) have recently provided striking evidence that chondroitin sulphate proteoglycans (CSPs), component molecules of the extracellular matrix (ECM), may play an important role in gating ocular dominance plasticity. CSP-rich ECM has been shown to inhibit axon regeneration in vivo (Davies et al., 1999). Thus Pizzorusso et al. (2002) hypothesized that CSPs might play a similar role in the primary visual cortex, suppressing neurite outgrowth to contribute to the closure of the critical period. Consistent with this idea, CSPs in the primary visual cortex increasingly aggregate into perineuronal nets over the timecourse of the critical period. The consequence of enzymatic degradation of CSP chains in the primary visual cortex of adult rats is surprising

433 and dramatic: when combined with MD, this
434 treatment results in a substantial shift in cortical
435 responses toward the nondeprived eye. In normal
436 adult rats, of course, MD of the same duration has
437 no effect. Thus, in V1, as has been well established in
438 the spinal cord, anatomical plasticity appears to be
439 critically dependent upon a permissive substrate for
440 neurite outgrowth.

441 An understanding of the specific mechanisms by
442 which CSPs regulate ocular dominance plasticity, and
443 knowledge of how these mechanisms interact with
444 those governed by intracortical inhibition, await
445 further experiments. However, the importance of the
446 CSPs in regulating V1 plasticity underscores the
447 importance of structural changes in serving as a long-
448 lasting storage mechanism for changes that occur
449 during ocular dominance plasticity.

450

451

452 Discussion

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454 Our understanding of the molecular mechanisms
455 underlying ocular dominance plasticity has expanded
456 rapidly in recent years, hastened both by novel
457 molecular techniques (as in Mower et al., 2002) and
458 the characterization of a murine model for ocular
459 dominance plasticity (Gordon and Stryker, 1996).
460 Progress in elucidating the signal transduction
461 mechanisms contributing to ocular dominance
462 plasticity has been particularly rapid, and findings
463 from experiments delineating the factors regulating
464 the timing of the critical period are entirely novel.

465 Of course, many outstanding questions remain.
466 Two areas are likely to yield significant research
467 advances in coming years. First, too little is known
468 about the many steps that must intervene between
469 rapid electrophysiological plasticity and subsequent
470 anatomical changes. Novel imaging techniques,
471 allowing anatomical changes to be visualized in real
472 time, combined with the use of KO and transgenic
473 mice, offers much promise of a more complete
474 understanding of the mechanisms underlying the
475 complete timeline of evolving synaptic change.
476 Second, more fully harnessing the potential of murine
477 genetics offers the distinct possibility of accelerating
478 the discovery of important molecular players in
479 ocular dominance plasticity. While studies of existing
480 KO mice have been very fruitful, they lean heavily on

in vitro studies to identify promising candidate
molecules. Forward genetic screens of mice deficient
in ocular dominance plasticity offer the hope of
rapidly uncovering molecular mechanisms in an
unbiased fashion.

Abbreviations

BDNF	brain-derived neurotrophic factor
CPG-15	candidate plasticity gene 15
CREB	cyclic AMP response element binding protein
CSP	chondroitin sulphate proteoglycan
ECM	extracellular matrix
ERK	extracellular signaling related kinase
GAD	glutamic acid decarboxylase
KO	knock-out
LGN	lateral geniculate nucleus
LTP	long-term potentiation
MCPG	(RS)-alpha-methyl-4-carboxyphenylglycine
mGluR	metabotropic glutamate receptor
MHC	major histocompatibility protein
NGF	neurotrophin growth factor
NT-3	neurotrophin 3
NT-4	neurotrophin 4
NMDA	N-methyl-D-aspartate
PKA	protein kinase A
tPA	tissue plasminogen activator
V1	primary visual cortex

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