

# Molecular Basis for Induction of Ocular Dominance Plasticity

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**ABSTRACT:** The most dramatic example of experience-dependent cortical plasticity is the shift in ocular dominance that occurs in visual cortex as a consequence of monocular deprivation during early postnatal life. Many of the basic properties of this type of synaptic plasticity have been described in detail. The important challenge that remains is to under-

stand the molecular basis for these properties. By combining theoretical analysis with experiments *in vivo* and *in vitro*, some of the elementary molecular mechanisms for visual cortical plasticity have now been uncovered. © 1999 John Wiley & Sons, Inc. *J Neurobiol* 41:

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The classic studies of Wiesel and Hubel first established that in normal kittens at about 1 month of age, most cortical neurons respond to stimulation of either eye, with varying degrees of ocular dominance. If an animal is allowed to mature in a normal visual environment, these binocular connections in the cortex are retained. However, if one eye is deprived of normal vision during the second postnatal month, there can be a dramatic change in the ocular dominance of the striate cortex such that the large majority of neurons lose responsiveness to the eye that had been deprived (Fig. 1) (Wiesel and Hubel, 1963). This selective depression of synaptic transmission in the cortex causes the animals to lose visual capabilities in the deprived eye (Wiesel, 1982). Similar forms of deprivation-induced synaptic depression have been observed in many species, including monkeys (Hubel

and Wiesel, 1977), rats (Fagioli et al., 1994), and mice (Gordon and Stryker, 1996). The important question remains as to how this dramatic change in cortical physiology comes about.

In the rancorous 36-year history of visual plasticity studies, there have been many conflicting claims and much controversy (not unlike the study of long-term potentiation today). This is not surprising considering the complexity of the system, the ambition of the investigators, and the challenge of making accurate and reproducible measurements from visual cortex *in vivo*. Fortunately, the smoke is beginning to clear. There is now general agreement on the key properties of ocular dominance plasticity that must be accounted for by any putative synaptic mechanism.

In this article we briefly review some of the properties of deprivation-induced synaptic depression in visual cortex. We then describe an experimental model for studying long-term synaptic depression, and discuss the molecular mechanisms for visual cortical plasticity that have been identified using that model.

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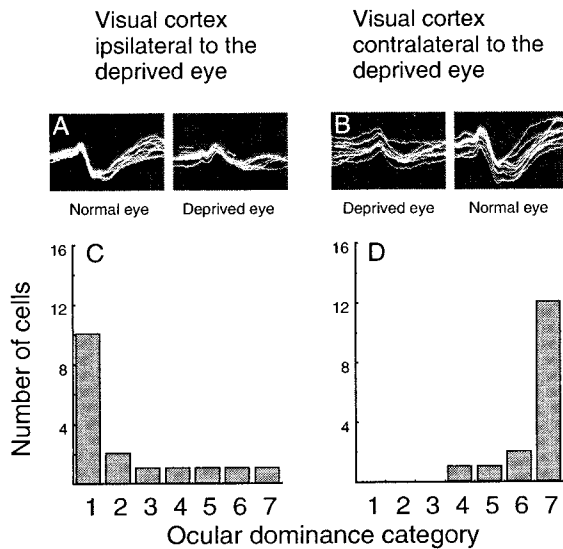
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**Figure 1** Deprivation-induced synaptic depression in the visual cortex. These data are reproduced from Wiesel and Hubel (1963). (A,B) Evoked potentials recorded from striate cortex in response to a brief light flash. At about the time of natural eye opening, this kitten had one eye covered with a translucent contact occluder that prevented patterned retinal stimulation and reduced general retinal illumination by about two log units. At the age of 2 months, the occluder was removed and the visually evoked potentials were measured. The reduced amplitude of the negative field potential evoked by deprived-eye stimulation reflects a depression of synaptic transmission in the cortex. (C,D) Ocular dominance assay. At 9 weeks of age, a kitten was monocularly deprived by lid suture for a period of 4 months. Single units were recorded along long electrode tracks and were assigned to one of seven ocular dominance categories. Cells in categories 1 and 7 are responsive exclusively to stimulation of the contralateral and ipsilateral eyes, respectively. Cells in categories 2–6 are binocular with varying degrees of ocular dominance.

### SOME KEY PROPERTIES OF DEPRIVATION-INDUCED SYNAPTIC DEPRESSION IN THE VISUAL CORTEX

1. Monocular deprivation produces greater synaptic depression than does binocular deprivation. As first noted by Wiesel and Hubel (1965), the effects of monocular deprivation are more severe than the effects of binocular deprivation. This observation gave rise to the venerable concept that the ocular dominance of cortical neurons is established and maintained by a process of activity-dependent competition between the synapses serving the two eyes. It should also be noted, however, that binocular deprivation does produce significant depression of visual re-

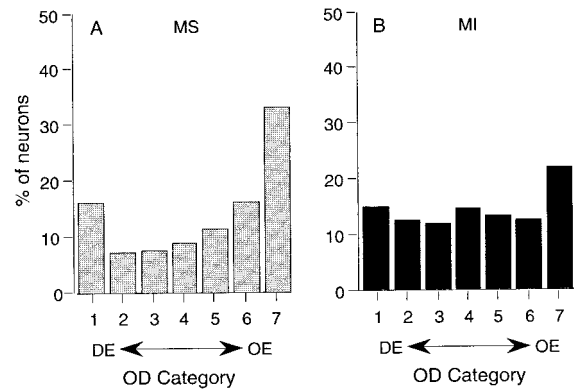
sponsiveness with a rapid time course (Freeman et al., 1981).

2. Deprivation-induced synaptic depression is most pronounced during a critical period of postnatal development. By starting periods of monocular deprivation at progressively older ages, Hubel and Wiesel (1970) first documented that ocular dominance plasticity is confined to a critical period which in the cat extends from 3 weeks to about 3 months of age. Similar findings have been made by a number of investigators, although the precise duration of the critical period depends on the length of time that the animals are monocularly deprived, and on the cortical layers under investigation. Plasticity ends first in layer IV, and last in layers II–III (Daw et al., 1992).
3. Deprivation-induced synaptic depression occurs rapidly at the height of the critical period. In their original studies, Wiesel and Hubel monocularly deprived animals for months. In later work, they found that robust effects were observed with as little as a week of deprivation (Hubel and Wiesel, 1970). Subsequent studies by many other investigators showed that as few as 8 h of deprivation could produce synaptic depression in the visual cortex (e.g., Freeman and Olson, 1982). The neurophysiological consequences are maximal after 48 h of monocular deprivation in animals at the height of the critical period (3–5 weeks of age) (Mower, 1991).
4. Deprivation produces structural changes in geniculocortical axons and synapses. In monkeys and cats (but not rats and mice), the afferents to cortex serving the two eyes are segregated into ocular dominance columns in layers IV and VI (Wiesel et al., 1974; Shatz et al., 1977). The territory innervated by afferents serving the deprived eye shrinks after weeks of monocular deprivation during the critical period (Hubel et al., 1977; Shatz and Stryker, 1978). Only 4 days of monocular deprivation are required to cause observable changes in the branching patterns of individual geniculocortical axon arbors serving the deprived eye (Antonini and Stryker, 1993). Visually deprived thalamocortical synapses are smaller and have an immature appearance (Tiemann, 1985).
5. Deprivation-induced synaptic depression is modulated by extrathalamic inputs that use acetylcholine, norepinephrine, and serotonin as neurotransmitters. The pioneering work of Kasamatsu and Pettigrew (1976) and Singer (1979) first suggested the possibility that extra-

- geniculate modulatory inputs to the visual cortex contribute to ocular dominance plasticity. It is now generally accepted that the neurotransmitters acetylcholine (ACh), norepinephrine (NE), and serotonin (5-HT) facilitate the deprivation-induced synaptic depression in visual cortex (Bear and Singer, 1986; Gordon et al., 1990; Gu and Singer, 1995; Wang et al., 1997).
6. Antagonists of *N*-Methyl-D-aspartate (NMDA) receptors inhibit deprivation-induced synaptic depression. Intracortical microinfusion of the NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (APV) during a period of monocular deprivation disrupts the ocular dominance shift (Kleinschmidt et al., 1987; Bear et al., 1990). Recent work using other methods to suppress NMDA receptor function and quantitative measurements of cortical activity indicates that this effect on plasticity is not simply accounted for by a reduction of postsynaptic visual responsiveness (Roberts et al., 1998; Daw et al., 1999). The data suggest an involvement of NMDA receptors in the mechanism of deprivation-induced synaptic depression.
  7. Deprivation-induced synaptic depression can be triggered by the activity of the deprived eye. There is much evidence that the synaptic depression caused by manipulation of visual experience is not simply a consequence of retinal inactivity. For example, if postsynaptic activity is blocked completely by intracortical infusion of a  $\gamma$ -aminobutyric acid receptor agonist (Reiter and Stryker, 1988) or a glutamate receptor antagonist (Bear et al., 1990), then the more active, nondeprived inputs become depressed relative to the deprived inputs. In addition, recent work has shown that total blockade of retinal activity produces less of an ocular dominance shift than deprivation only of patterned visual stimulation (Fig. 2) (Rittenhouse et al., 1999). These data suggest that the synaptic depression caused by monocular deprivation is actually driven by the residual activity in the visually deprived retina.

### HOMOSYNAPTIC LONG-TERM DEPRESSION MODEL

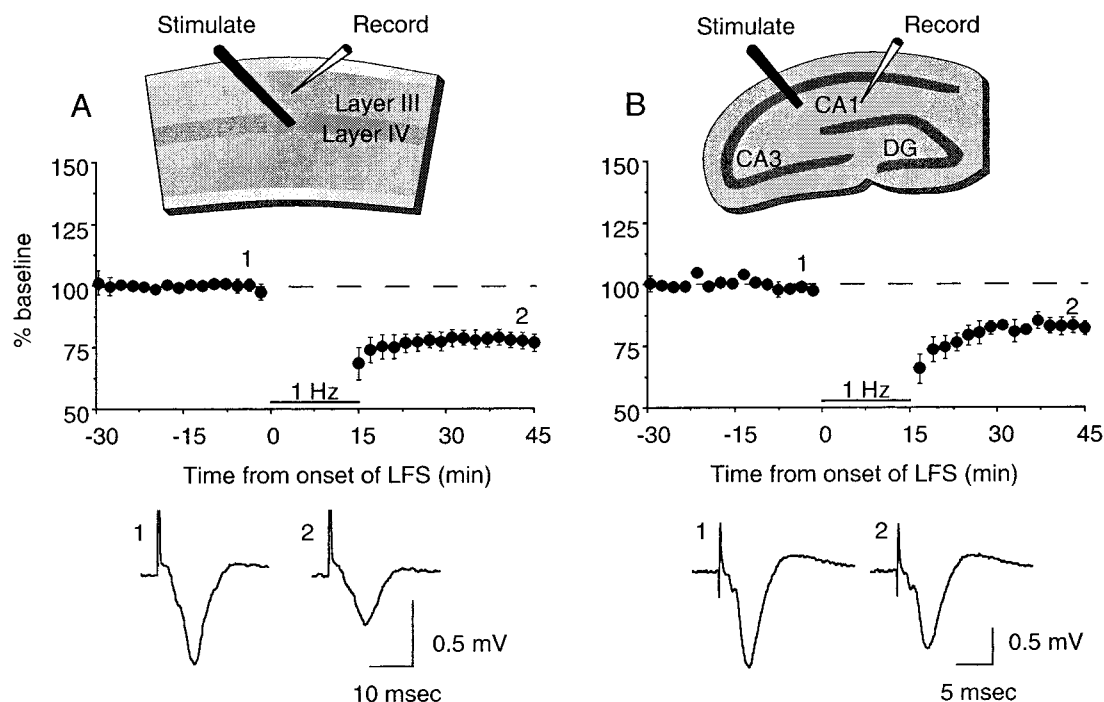
The last point listed above—that presynaptic activity is an important factor in triggering synaptic depression—is a distinguishing feature of a theory of synaptic modification that has been advanced to account for ocular dominance plasticity (Blais et al., 1998).



**Figure 2** Retinal activity in the deprived eye drives synaptic depression in visual cortex. These data are reproduced from Rittenhouse et al. (1999). (A) The effects of 2 days of monocular lid suture (MS) on ocular dominance in kittens at about 2 months of age. (B) The effects of 2 days of monocular inactivation (MI) produced by an intraocular injection of tetrodotoxin. The ocular dominance shift is significantly reduced in the MI group as compared to the MS group (MS group: 273 neurons recorded from 10 animals; MI group: 238 neurons recorded from 10 animals).

According to the BCM theory (Bienenstock et al., 1982), activation of a modifiable excitatory input will lead to an increase or decrease in synaptic effectiveness depending on whether the coincident activity of the postsynaptic neuron falls above or below a critical value, called the “modification threshold,” or  $\theta_m$ . The modification threshold is proposed to vary as a non-linear function of the average, integrated postsynaptic cortical activity. Therefore, the value of  $\theta_m$  is lower during binocular deprivation than during monocular deprivation. Consequently, the amount of synaptic depression triggered by presynaptic activity during binocular deprivation is less than during monocular deprivation (for a given level of postsynaptic response).

The conditions required for synaptic potentiation according to the BCM theory (and other “Hebbian” learning rules) are similar to those required for the induction of long-term potentiation (LTP) in the CA1 region of hippocampus (Kelso et al., 1986) and the visual cortex (Kirkwood and Bear, 1994). Pairing presynaptic activity with strong postsynaptic depolarization induces LTP. Therefore, it was hypothesized that the necessary condition for long-term synaptic depression (LTD) might be presynaptic activity that consistently fails to evoke (or correlate with) a postsynaptic response large enough to trigger LTP (Bear et al., 1987). This hypothesis has now been confirmed in both hippocampus and visual cortex (Artola and Singer, 1993; Bear and Kirkwood, 1996).



**Figure 3** Homosynaptic long-term depression in visual cortex and hippocampus. These data are reproduced from Kirkwood et al. (1993). Synaptic transmission in response to electrical stimulation of presynaptic axons is monitored using extracellular field potential recordings. In visual cortex (A) and hippocampus (B), 15 min of 1 Hz stimulation induces long-term depression of synaptic transmission.

Because the depression occurs only at the synapses that receive the presynaptic stimulation, the phenomenon is referred to as homosynaptic LTD.

The goal of studying homosynaptic LTD is to gain insight into the mechanisms of naturally occurring synaptic depression. LTD is a model. In studies of LTD, one attempts to emulate experience by using patterned electrical activation of synapses. To be convincing, LTD must be induced with conditioning stimulation that is sufficiently brief so as to distinguish synaptic plasticity from baseline drift, and sufficiently strong so as to distinguish a synaptic modification from baseline fluctuations. Although in these respects LTD is different from deprivation-induced synaptic depression, which occurs more gradually, the hope is that by studying it we can reveal the mechanisms that contribute to ocular dominance plasticity.

Below, we describe some of the salient features of homosynaptic LTD and comment on their possible relation to naturally occurring synaptic depression.

1. Homosynaptic LTD occurs in response to presynaptic activity that consistently fails to strongly activate postsynaptic neurons. Although homosynaptic LTD can be elicited by a
2. LTD is most pronounced during a critical period of postnatal development. At Schaffer collateral synapses in the hippocampus (Dudek and

number of different types of conditioning stimulation, a common protocol is to apply long trains (e.g., 15 min) of synaptic stimulation at low frequencies (e.g., 1 Hz) and at stimulation intensities that are just subthreshold for synaptically evoking postsynaptic action potentials (Fig. 3) (Dudek and Bear, 1992; Kirkwood et al., 1993). Another approach has been to precede synaptic stimulation with a postsynaptic depolarizing voltage pulse (Debanne et al., 1994) or action potential (Markram et al., 1997). The low-frequency stimulation (LFS) protocol was designed to emulate the monocular deprivation situation (input activity that does not evoke a strong postsynaptic response), whereas the associative protocols may model strabismus (uncorrelated activity patterns from the two eyes). One common feature of these different approaches for inducing LTD is that they both lead to a critical level of NMDA receptor activation and postsynaptic calcium entry (see below).

- Bear, 1993) and layer IV synapses in sensory neocortex (Dudek and Friedlander, 1996; Feldman et al., 1998), it is well established that there is a progressive decline in LTD with postnatal age. The decline in layer IV LTD correlates well with the decline in deprivation-induced synaptic depression in this layer. A detailed analysis of LTD in the superficial layers of visual cortex has not yet been performed, but it appears that there is a quantitative reduction (if not complete elimination) of LTD with increasing age (Kirkwood et al., 1997; Sermasi et al., 1999).
3. One form of homosynaptic LTD is induced by postsynaptic NMDA receptor activation and a second form depends on metabotropic glutamate receptor activation. Under most experimental conditions, induction of homosynaptic LTD in the CA1 region and neocortex is inhibited when NMDA receptors are blocked (e.g., Kirkwood et al., 1993). Indeed, the appropriate level of NMDA receptor activation apparently is sufficient to induce LTD (Kandler et al., 1998). (The level of NMDA receptor activation must be appropriate, since strong activation induces synaptic potentiation instead.) The inhibition of this LTD induction mechanism may account for why NMDA receptor antagonists prevent deprivation-induced synaptic depression. However, there is now good evidence from studies of hippocampus that a second, and perhaps mechanistically distinct, form of LTD can be evoked with LFS via activation of postsynaptic phosphoinositide-coupled metabotropic glutamate receptors (mGluRs) (Bolshakov and Siegelbaum, 1994; Oliet et al., 1997). Although it has not been fully characterized, there is some evidence that the mGluR-dependent form of LTD is also expressed in visual cortex (Haruta et al., 1994; Hensch and Stryker, 1996). It may be significant that glutamate-stimulated phosphoinositide hydrolysis peaks in visual cortex at the height of the critical period and declines with a time course similar to that for ocular dominance plasticity (Dudek and Bear, 1989). A parallel, non-NMDA receptor-dependent, mechanism for LTD induction may account for why synaptic depression of active cortical inputs occurs when postsynaptic electrical activity is blocked completely (Reiter and Stryker, 1988; Bear et al., 1990).
  4. The magnitude of LTD is reduced in visual cortex that has been binocularly deprived. As a test of the proposal that the value of  $\theta_m$  is

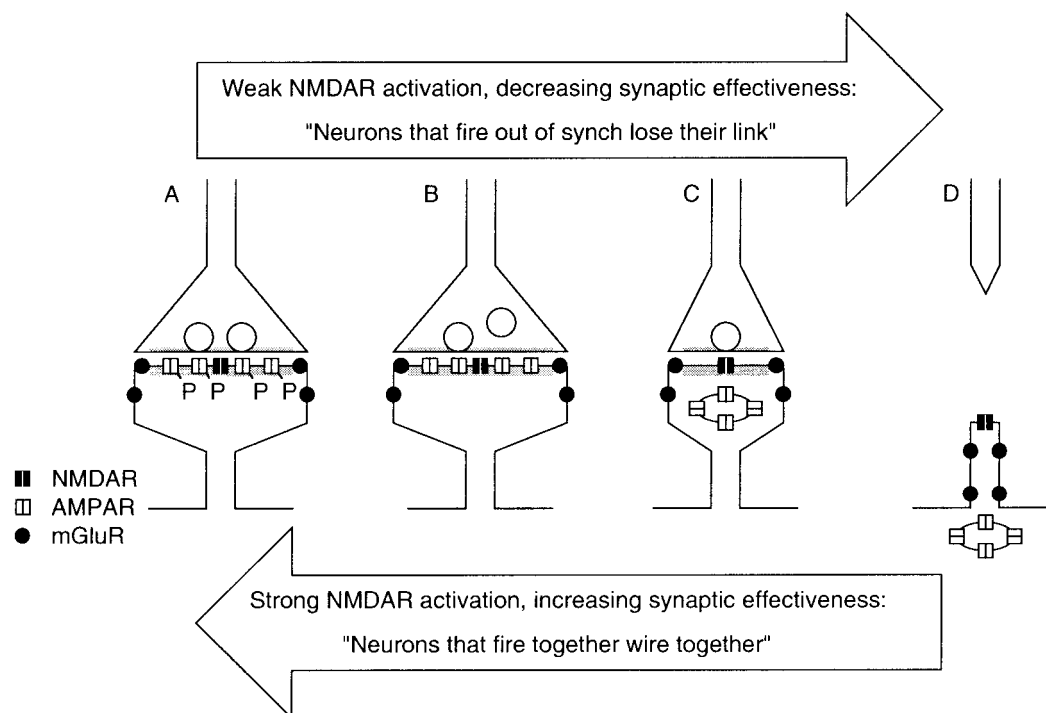
related to the history of cortical activity, LTD and LTP have been studied in the visual cortex of visually deprived animals (stimulating layer IV or the white matter, and recording synaptic responses in layer III). A consistent finding is that LTD magnitude is reduced in animals that have been binocularly deprived (by dark-rearing) (Kirkwood et al., 1996; Sermasi et al., 1999). Although the results are more variable, it appears that brief (7- to 14-day) binocular deprivation also reduces LTD amplitude (M. Rioult and M. Bear, unpublished observations; Sermasi et al., 1999). Experience-dependent changes in the molecular composition and function of NMDA receptors are one likely basis for this difference in the properties of synaptic plasticity in binocularly deprived animals (Quinlan et al., 1999). The fact that presynaptic activity causes less synaptic depression when average cortical activity is reduced may account in part for why deprivation of both eyes causes less synaptic depression than deprivation of one eye.

5. Acetylcholine, norepinephrine, and serotonin modulate LTD in visual cortex. Recent work has shown that bath application of ACh, NE, and 5-HT agonists can produce a substantial facilitation of LTD in visual cortex (Kojic et al., 1997; Kirkwood et al., 1999). Although the mechanism remains to be investigated in detail, the modulation may partly be accounted for by increasing the gain of NMDA receptor-dependent LTD. The finding that ACh and NE facilitate LTD in visual cortex in a qualitatively similar way suggests an explanation for the finding that cholinergic and noradrenergic inputs to cortex apparently substitute for one another in the modulation of ocular dominance plasticity (Bear and Singer, 1986).

## MOLECULAR MECHANISM OF HOMOSYNAPTIC LONG-TERM DEPRESSION

The LTD model in visual cortex clearly shares many of the key properties of deprivation-induced synaptic depression, and it clearly has considerable explanatory power. It would be unlucky indeed if the eventual understanding of the molecular basis for the developmental decline in LTD did not yield at least a partial explanation for the developmental decline in ocular dominance plasticity. There are also differences between LTD and ocular dominance plasticity, however. The most striking difference is that unlike ocular





**Figure 4** Model connecting the mechanisms of homosynaptic depression and anatomical plasticity.

dominance plasticity, no clear structural consequences of LTD have yet been established. Of course, LTD is generally studied over a time period of a few hours when structural modifications are expected to be subtle, even after monocular deprivation *in vivo*. Thus, the working hypothesis is that the mechanisms of LTD reflect an early consequence of visual deprivation, which are followed at longer intervals by gross changes in synaptic structure.

What are the mechanisms of homosynaptic LTD? As we mentioned above, it has been firmly established in both hippocampus and visual cortex that one induction mechanism involves activation of NMDA receptors, and a second mechanism requires activation of mGluRs. The molecular events that occur downstream from glutamate receptor activation have been worked out mainly in the hippocampus, and mainly for the NMDA receptor-dependent form of LTD. In this case, it has been established that LTD requires a modest or prolonged rise in postsynaptic calcium concentration and a net dephosphorylation of postsynaptic phosphoproteins (for review, see Bear and Abraham, 1996). One of the dephosphorylated proteins is the postsynaptic AMPA receptors (Lee et al., 1998). Dephosphorylation of AMPA receptors decreases glutamate-evoked currents, and therefore is one likely mechanism for LTD (Roche et al., 1994). There is also evidence that LTD is accompanied by an

increase in synaptic failures (Stevens and Wang, 1994). Reduced probability of neurotransmitter release or the loss of postsynaptic clusters of AMPA receptors could explain a decrease in the reliability of synaptic transmission. Similar changes in synaptic reliability after LTD have been observed in visual cortex (Torii et al., 1997).

Figure 4 presents a model that, while speculative, is consistent with current data on the mechanism of synaptic depression at glutamatergic synapses. A full complement of postsynaptic glutamate receptors (NMDA, AMPA, and mGluR) and basal phosphorylation of the AMPA receptors [Fig. 4(A)] characterize a functional synaptic connection. Modest activation of NMDA receptors, occurring when presynaptic glutamate release is not correlated with a strong postsynaptic response, leads to the activation of postsynaptic phosphatases, the dephosphorylation of AMPA receptors, and a depression of synaptic transmission [Fig. 4(B)]. These postsynaptic changes are accompanied by a reduction in glutamate release probability, perhaps mediated by a retrograde messenger. AMPA receptors, unprotected by phosphorylation, are then internalized over time [Fig. 4(C)]. Although there is no direct evidence for receptor internalization with LTD, there is considerable evidence that activity regulates the surface expression of AMPA receptors (Turrigiano et al., 1998; Liao et al., 1999; Lissin et al.,

1999). In the absence of AMPA receptors, the fast synaptic response to glutamate is mediated exclusively by NMDA receptors. Because NMDA receptors pass little synaptic current at the resting membrane potential, such synapses are described as postsynaptically silent (Liao et al., 1995; Issac et al., 1995). At the developing neuromuscular junction, it has been established that the loss of postsynaptic receptors precedes the physical elimination of the presynaptic axon (Colman et al., 1997). We suggest that the same thing occurs at glutamatergic cortical synapses that have lost postsynaptic AMPA receptors [Fig. 4(D)].

The model in Figure 4 was developed to account for the depression and loss of functional synapses. However, it should be noted that reversing the order of illustrations (Fig. 4(D) to 4(A)) represents the changes that occur during maturation of glutamatergic synapses in several systems (Durand et al., 1996; Wu et al., 1996), a process that is triggered to occur by strong NMDA receptor activation. Synaptic potentiation and depression are two sides of the same coin.

## DISCUSSION

Activity arising from an eye that is deprived of normal vision can trigger a decrease in synaptic effectiveness in the visual cortex (Rittenhouse et al., 1999). How does this synaptic depression occur? By emulating in a slice preparation the conditions that produce modifications *in vivo*, it has been possible to establish some of the molecular mechanisms that trigger deprivation-induced synaptic depression. It is quite clear that one mechanism involves the activation of postsynaptic NMDA receptors, a rise in postsynaptic calcium, and activation of protein phosphatases. A second mechanism may include activation of postsynaptic mGluRs.

We have highlighted the many similarities of LTD and ocular dominance plasticity. However, there have been reports of some pharmacological and genetic manipulations in mice that affect the two phenomena differently. For example, both the drug  $\alpha$ -methyl-4-carboxyphenylglycine (MCPG) (Hensch and Stryker, 1996) and the genetic deletion of one regulatory subunit of adenylyl cyclase (Hensch et al., 1998) can impair one form of LTD in visual cortical slices without having effects on ocular dominance plasticity. Conversely, deletion of one isoform of glutamic acid decarboxylase impairs ocular dominance plasticity without a gross change in LTD (Hensch et al., 1998). These findings do not mean that the mechanisms of LTD are not used in ocular dominance plasticity, however. First, it is now clear that there are multiple

mechanisms of LTD, and this fact has not been taken fully into account in these studies (e.g., MCPG has no effect on NMDA receptor-dependent LTD) (Huber et al., 1997). Second, some of the manipulations (e.g., genetic deletion of isoforms of adenylyl cyclase and glutamic acid decarboxylase) do not disable the elementary mechanisms of synaptic plasticity, but instead alter the experimental conditions required to engage them. Even if LTD and deprivation-induced synaptic depression use identical molecular mechanisms, their routes of induction (LFS or monocular deprivation) may be differentially susceptible to genetic and other manipulations (for further discussion, see Bear, 1998).

It is our opinion that the weight of the evidence strongly favors the hypothesis that the mechanisms revealed by the study of LTD contribute to the synaptic depression in visual cortex that is caused by monocular deprivation. Obviously, other mechanisms may also contribute as well. Nonetheless, the LTD model can and should be exploited to understand the molecular chain of events that lie downstream from glutamate receptor activation, how physiological plasticity and structural plasticity are related, how synaptic depression is regulated during development, and how synaptic plasticity is modulated by behavioral state.

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Note added in proof: Carroll et al. (Nat. Neurosci 2: 454–460) have now obtained evidence using hippocampal cell culture that LTD is in fact associated with the loss of AMPA receptors at the synapse.

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