Depressed from deprivation? Look to the molecules…

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Heynen and colleagues provide direct evidence for the molecular cascade underlying monocular deprivation, also providing a critical link between changes in sensory experience and a well studied form of synaptic plasticity, long-term depression.

Sensory experience can dramatically alter the structure and function of neural circuits in the developing neocortex. Despite advances in understanding the effects of sensory experience on cortical function, the molecular events that underlie experience-dependent plasticity remain a mystery. In this issue, Heynen *et al.*[1] now provide some of the first direct evidence for a molecular cascade that underlies a classic form of plasticity in the visual system—the shift in ocular dominance that occurs in visual cortex after one eye is closed during early postnatal life. This evidence provides a long-awaited, critical link between changes in sensory experience and a well-studied form of synaptic plasticity, long-term depression (LTD).

The first evidence for the shaping of ocular dominance columns by visual experience was provided by Wiesel and Hubel[2]. They discovered that if one eye is closed for a period during development (monocular deprivation, or MD), then an abnormally large majority of cortical neurons become responsive to the open eye, rather than exhibiting close to equal responsiveness to inputs from each eye. Because correlated pre- and postsynaptic activity is thought to be required for the strengthening of synapses in the developing visual cortex, it is generally assumed that this activity-dependent refinement follows Hebb's postulate of learning: the synaptic efficacy of a presynaptic neuron will increase if it persistently causes the postsynaptic neuron to fire[3]. A correlate of Hebbian plasticity is that the synaptic efficacy between neurons whose activity is anti-correlated will be weakened over time. Because the two major forms of long-term plasticity in the hippocampus—long-term potentiation (LTP) and long-term depression (LTD)—are based on Hebbian rules, there has been much speculation that LTP and LTD might be the cellular mechanisms underlying synaptic refinement in the developing visual cortex[4].

Over the last decade, there has been tremendous progress in understanding the molecular basis of NMDA receptor-dependent LTP and LTD. In addition, much correlative evidence has suggested that these forms of long-term plasticity might underlie experience-dependent refinement of connections in sensory cortex. Consistent with this idea, NMDA receptor-dependent LTP and LTD can be induced in slices of visual cortex from animals undergoing activity-dependent refinement only during the critical period for ocular dominance plasticity[5,6]. However, since most LTP/LTD experiments have been performed in acute slice preparations, it has been hotly debated as to whether long-term plasticity as measured in slices in response to potentially artificial patterns of stimulation represents a phenomenon that underlies synaptic plasticity *in vivo* in response to changes in sensory experience. The ultimate challenge has been to relate the mechanisms of LTP and LTD to naturally-occurring plasticity in a sensory system.

In this issue, Heynen *et al.*[1] have met this challenge for MD and LTD. In order to determine if MD induces LTD, Bear and colleagues set out to meet the two criteria that demonstrate whether two biological processes occur by the same mechanism: mimicry and occlusion. In a series of experiments, they demonstrate that brief MD in rodents causes the same molecular and functional changes as homosynaptic LTD; this satisfies the requirement of mimicry. They then meet their second requirement by showing that synaptic depression caused by MD occludes subsequent induction of LTD.

In order to demonstrate mimicry, Heynen *et al.*[1] cleverly used a molecular fingerprint for LTD to show that even brief MD causes the same molecular changes as those induced by LTD. Previous work has shown that LTD initiates a unique pattern of phosphorylation of specific residues on the AMPA receptor subunits GluR1 and GluR2. During LTD, the serine 831 residue (Ser831) on GluR1 is unaltered, Ser845 on GluR1 is selectively and persistently dephosphorylated, and Ser880 on GluR2 is selectively and persistently phosphorylated[7–9]. In addition to changes in phosphorylation, AMPA receptors are also rapidly internalized following LTD induction[10]. These unique molecular changes can be used as a fingerprint for NMDA receptor-dependent homosynaptic LTD.

Heynen *et al.*[1] show that LTD and MD cause many of the same functional changes in the deprived visual cortex. LTD induction *in vivo* at the geniculocortical synapse led both to depression of visually evoked potentials (VEPs) and to reliable dephosphorylation of Ser845 on GluR1, whereas Ser831 remained unaltered. Conversely, brief MD led to rapid depression of deprived-eye responses. This deprivation-induced synaptic depression coincided with dephosphorylation of Ser845, increased phosphorylation of Ser880 and unchanged phosphorylation of Ser831 (**Fig. 1**). These changes depended on NMDAR activation, were restricted to a critical period of postnatal development, and were comparable in magnitude to the alterations in phosphorylation caused by LTD induction at the geniculocortical synapse. Finally the authors found that brief MD decreased AMPAR surface expression in visual cortex (**Fig. 1**). This decrease in surface AMPARs was not simply a consequence of reduced retinal activity, but rather was caused by the uncorrelated noise that drives deprivation-induced synaptic depression[11].

The second criterion to prove that MD and LTD occur by the same mechanism was to show

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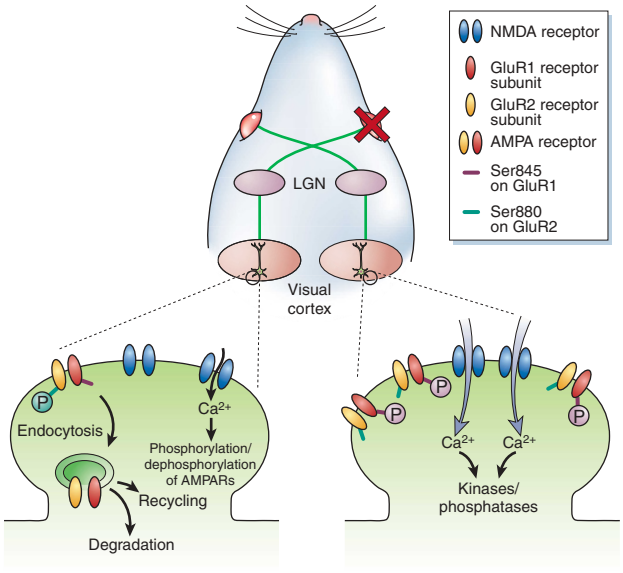

Figure 1 Schematic diagram of the molecular fingerprint for LTD that Heynen *et al.*[1] show is induced by MD in rodents.

that MD occludes the synaptic expression of LTD. If MD uses the same cellular mechanisms as LTD, then the magnitude of LTD should be reduced in the deprived area of visual cortex following MD. Consistent with this prediction, the magnitude of LTD was significantly reduced in the cortex contralateral to the deprived eye.

On the basis of both mimicry and occlusion, the authors conclude that MD induces LTD in visual cortex, providing the first proof of a molecular basis for the long-term plasticity induced *in vivo* by visual deprivation. Recently, Feldman and colleagues reported that whisker deprivation leads to LTD in corresponding cortical barrels in the somatosensory cortex[12]. It will be interesting to see if this deprivation-induced LTD in somatosensory cortex is mediated by the same molecular mechanisms as Heynen and colleagues show for MD in the visual cortex. Taken together, these results now provide the long-awaited evidence that should quiet skeptics who held that LTD is simply a slice phenomenon resulting from artificial patterns of electrical stimulation.

Although this paper elegantly demonstrates that MD induces LTD, the authors emphasize that it does not unequivocally show that the mechanisms of LTD are the only mechanisms underlying MD. Indeed, there are likely to be additional mechanisms that contribute to the effects of MD; for example, there are multiple forms of LTD, and there are examples in which altering LTD has no effect on ocular dominance plasticity and vice versa[13]. Nevertheless, the primary implication of this paper is that LTD is a compelling model that will help to reveal the cascade of cellular events that occurs from the decreased activity in visual cortex resulting from MD to the expression of deprivation-induced synaptic depression and subsequent structural changes. Indeed, one of the most exciting remaining mysteries in this process is how MD initiates the structural changes that underlie its effects on ocular dominance plasticity[14]. To date, LTD has not been shown to result in a loss of connectivity in the central nervous system. Now that there is a strong link between MD and LTD *in vivo*, future work is sure to focus on possible mechanisms whereby LTD could initiate the synapse elimination that follows MD. Finally, given the defects in LTD and synapse elimination that occur in several forms of developmental disorders, including fragile-X syndrome[15], it is clear that understanding the molecular basis of experience-dependent plasticity will have relevance far beyond the question of how MD leads to blindness.

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Crystallizing our understanding of partial agonists

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A powerful combination of X-ray crystallography and single-channel current measurements provides new insights into the mechanism by which the binding of agonists opens the AMPA-type glutamate receptor in the central nervous system.

Out on a distant domain, perhaps tens of angstroms above the lipid bilayer, an amino acid docks into its binding pocket. The binding perturbs this multimeric membrane protein, initiating a rapid sequence of events that culminates in the opening of an integral ion pore that passes some 10^7 ions per second. Such excitatory chemical transmission is the predominant means by which neurons in the central nervous system communicate, yet despite decades of intensive research, fundamental aspects of the activation process remain an enigma.

One unresolved issue relates to the mechanism of action of partial agonists. Partial agonists are ligands that can activate the receptor, but not as well as a full agonist. Understanding the actions of partial agonists has long promised to take us closer to unraveling the molecular basis of activation. In this

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