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Bidirectional synaptic plasticity: from theory to reality

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Theories of receptive field plasticity and information storage make specific assumptions for how synapses are modified. I give a personal account of how testing the validity of these assumptions eventually led to a detailed understanding of long-term depression and metaplasticity in hippocampal area CA1 and the visual cortex. The knowledge of these molecular mechanisms now promises to reveal when and how sensory experience modifies synapses in the cerebral cortex.

Keywords: long-term depression; metaplasticity; visual cortex; ocular dominance plasticity; Hebb; Bienenstock–Cooper–Munro (BCM) theory

1. HEBB SYNAPSES AS A BASIS FOR RECEPTIVE FIELD PLASTICITY IN VISUAL CORTEX

How are synapses in the cerebral cortex modified by experience to store information? Important clues have come from studies of how neuronal activity changes in response to a changing environment. A consistent finding is that as the environment changes and new information is stored, cells gain responsiveness to some stimuli and lose responsiveness to others. In other words, neuronal receptive fields are modified by experience. These changes in receptive fields reflect synaptic modifications that, distributed over many neurons, store information. Thus, we can reframe the question: what is the synaptic basis of receptive field plasticity in the cerebral cortex?

A good example of receptive field plasticity can be found in the visual cortex during early postnatal life. When a visual cortical neuron receives information from the two eyes that is *correlated*, as is often the case during normal binocular vision, the cell becomes responsive to both eyes. When the correlation breaks down, as occurs during a period of monocular deprivation or strabismus, then the cell becomes monocularly responsive in a 'winner-takes-all' fashion. Thus, input patterns can *associate* or *compete* depending on how well they are correlated (Wiesel 1982). The correlation detector must be the postsynaptic neuron, because it has available information from both eyes, and a reasonable assumption is that the degree of correlation among converging inputs is reflected in the firing rate of the neuron.

In 1949, Donald Hebb postulated that associative memories are formed in the brain by a process of synaptic modification that strengthens connections when presynaptic activity correlates with postsynaptic firing (Hebb 1949). Thus, 'Hebb synapses' were enthusiastically embraced as a likely basis for receptive field plasticity in the visual cortex (and receptive field plasticity in the visual cortex was enthusiastically embraced as a model for associative memory). However, it was also immediately apparent that 'Hebbian' modification alone would not be sufficient to account for receptive field plasticity—there must also exist a synaptic basis for weakening connections when presynaptic activity is poorly correlated with postsynaptic firing. Thus, in 1973 Gunther Stent made the influential proposal that connections weaken when they are inactive at the same time that the postynaptic neuron is active (owing to the influence of competing inputs). According to this way of thinking, postsynaptic activity, driven by a set of well-correlated inputs, initiates the physiological processes that potentiate the active synapses *and* depress the inactive ones (which, interestingly, Stent envisaged to be the stabilization or elimination of postsynaptic receptors). To account for the effects of the behavioural state on visual cortical plasticity, Wolf Singer (1979) added the provision that postsynaptic activity has to cross a threshold to be permissive for synaptic modifications. Singer, also ahead of his time, made the further suggestion that the permissive postsynaptic factor for receptive field plasticity is dendritic calcium entry.

2. HIPPOCAMPUS AND VISUAL CORTEX COLLIDE

I joined Wolf Singer as a post-doctoral student in 1984 to investigate the modulation of visual cortical plasticity by cholinergic and noradrenergic inputs. Modulation seemed like a ripe target for establishing a molecular mechanism for visual cortical plasticity. Although I accepted the necessity of assuming that Hebb synapses account for receptive field plasticity, such theories seemed very abstract in the absence of a clue as to how the active postsynaptic neuron could distinguish active from inactive inputs and reward and punish them, respectively. Suddenly, this situation changed, because of three key discoveries made in hippocampal area CA1 between 1983 and 1986. First, induction of LTP became NMDAR and Ca^{2+} dependent; second, NMDARs became detectors of coincident presynaptic and postsynaptic activity; third, and most importantly, LTP became Hebbian (reviewed

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by Bliss & Collingridge 1993; see also Collingridge 2003). These studies showed that an active (strongly depolarized) neuron could recognize a simultaneously active presynaptic input by the local Ca^{2+} flux through the postsynaptic NMDARs, and reward it by making this synapse stronger.

These discoveries had a huge impact on how we subsequently approached the problem of visual cortical plasticity. LTP became a molecular metaphor for Hebbian plasticity. We started to pay close attention to what was happening in the hippocampus to gain insights into the molecular basis for receptive field plasticity. Additionally, of course, we now had a potential mechanism for Hebbian modifications based on the properties of NMDARs. People started infusing the NMDAR antagonist APV everywhere Hebbian modifications were suspected to occur—into rat hippocampus during learning; into frog optic tectum during development; and, in our case, into kitten visual cortex during a period of monocular deprivation—and there was universal agreement: blocking NMDARs disrupts experience-dependent synaptic plasticity (Morris *et al.* 1986; Cline *et al.* 1987; Kleinschmidt *et al.* 1987).

As Stent had recognized many years before, however, Hebbian modifications are, at most, only half the story. There must also be mechanisms for synaptic depression, certainly to account for the dramatic effects of monocular deprivation in the visual cortex. Students of visual cortical plasticity, unlike many of our hippocampal colleagues, shared a deep conviction that there must also be a mechanism of LTD. However, I began to have doubts about Stent's specific proposal. According to Stent, synaptic weakening occurs by *heterosynaptic depression*—activity in one set of synpases leads to depression of a second, inactive set. Yet, many studies of LTP in CA1 (my focus, for reasons stated above) had failed to reveal this phenomenon (although it had been reported to occur in the dentate gyrus by Abraham & Goddard (1983)). Closer to home, studies in Singer's laboratory, using a manipulation of visual experience called reverse-suture, showed that monocular deprivation could rapidly depress synaptic responses even when postsynaptic neurons were relatively silent. This finding seemed to violate the principle that postsynaptic activation beyond a threshold is required for receptive field plasticity. I also began to question the precise role of dendritic Ca^{2+} in visual cortical plasticity, which now seemed more likely to be instructive than permissive.

3. A PHYSIOLOGICAL BASIS FOR THE BIENENSTOCK–COOPER–MUNRO THEORY

I started to consider alternative ideas, and became interested in a different theory for visual cortical receptive field plasticity, developed by theoretical physicist Leon Cooper and his colleagues. Therefore, when Leon and Ford Ebner offered me a faculty position in their Centre for Neural Science at Brown University, I gladly accepted. We spent much of 1986 discussing the theory, the new understanding of the biology of synaptic transmission in the cortex, and how these might be related. Because we spoke different languages (those of mathematics and biology), these conversations could be painful (eased occasionally by Leon's stash of fine single malt). However, as we came to understand each other, a very interesting picture started to emerge.

As in previous Hebbian models, Cooper *et al.* (1979) had suggested that active synapses grow stronger when postsynaptic activity exceeds a 'modification threshold', θ_m. However, instead of assuming that quiet synapses simultaneously depress, they proposed that depression occurs at presynaptically *active* synapses when postsynaptic activity falls below θ_m (but remains above a lower threshold, defined as zero). Thus, the proposal was that presynaptic activity triggers synaptic depression or potentiation depending on the concurrent level of postynaptic activity (i.e. the degree of correlation). To explain competition and provide stability, Bienenstock *et al.* (1982), in what is now called the BCM theory, made the additional proposal that the value of θ_m varies as a function of the history of integrated postsynaptic activity. As average activity falls or rises, so does the value of θ_m. I was particularly attracted to this 'sliding threshold' idea, as it seemed to account for the effects of reverse-suture in visual cortex.

How might such a form of modification be implemented by glutamatergic synapses? I considered the possibility that θ_m corresponds to the threshold level of postsynaptic response at which NMDAR-dependent Ca^{2+} flux is sufficient to induce LTP. Two interesting predictions followed. First, input activity that consistently fails to activate postsynaptic neurons (elevate postsynaptic Ca^{2+}) sufficiently to induce LTP should induce LTD instead. Second, the threshold level of stimulation required to achieve LTP should vary depending on the history of cellular activity, which I reasoned could be accomplished by alterations in the voltage- or glutamate-sensitivity of NMDARs. These proposals were published (Bear *et al.* 1987), and testing them was the first priority of my newly established laboratory.

4. HOMOSYNAPTIC LONG-TERM DEPRESSION IN HIPPOCAMPUS

My goal was to establish models of synaptic plasticity in slices of visual cortex, copying the approach that had been so successful in area CA1 of the hippocampus. At the time, few data were available on LTP in the neocortex, and I quickly discovered why—they were very difficult to elicit (a problem later solved in my laboratory by Alfredo Kirkwood). Fortunately, in the meantime, Serena Dudek joined me as a graduate student. Serena had spent some time in Gary Lynch's laboratory, so she arrived with considerable hippocampal slice experience. Therefore, we decided to search for LTD in area CA1, where the Hebbian properties of LTP had already been established. Our approach was to emulate the conditions that, in theory, should produce LTD—lots of presynaptic activity under conditions that yield postsynaptic responses too weak to induce LTP. Of course, this was electrophysiology for the resource challenged; we were recording extracellular synaptic field potentials, and had no way of directly manipulating postsynaptic voltage. However, it had been established that LTP is reliably induced by high-frequency stimulation of a bundle of Schaffer collateral axons because the temporal summation of synaptic responses strongly depolarizes postsynaptic neurons in CA1. Therefore, our approach was to vary the frequency, intensity

and duration of the synaptic stimulation, searching for the sweet spot that might yield LTD. This is obviously a large parameter space, and despite the additional help of Joel Gold, a Brown undergraduate, many months of failure ensued. However, we were determined. This was one of those cases where to see it, one had to believe in it. We were believers.

The breakthrough came in 1991. We discovered that at an intensity just below threshold for producing population spikes, prolonged stimulation (900 pulses) at 0.5–3 Hz reliably induced LTD in CA1. However, there were some immediate reasons for concern. Previous reports in the literature suggested that similar types of stimulation do not alter baseline synaptic transmission (which we ascribed to significant differences in experimental conditions). More worryingly, however, these same studies reported that a 1 Hz stimulation could be quite effective in reversing LTP if it was delivered shortly after induction (Barrionuevo *et al.* 1980; Staubli & Lynch 1990; Fujii *et al.* 1991). This retrograde disruption of LTP, a phenomenon called depotentiation, could also be produced by such non-specific manipulations as temporary anoxia (Arai *et al.* 1990*b*), bath application of adenosine (Arai *et al.* 1990*a*) or inducing seizure activity (Hesse & Teyler 1976).

Therefore, the challenge became to convince ourselves, and what we anticipated would be a very critical audience of hippocampal physiologists, that LTD indeed was a form of synaptic modification. After all, there are several manipulations that can make synaptic transmission depress that are not synaptic plasticity (frying the fibres with too much stimulation current or bumping the air table, for example). Global changes in slice health were eliminated by demonstrating that the LTD was input specific, and therefore *homosynaptic*. To address the concern of using so many stimulus pulses, Serena varied the frequency while holding the number of pulses constant. Remarkably, she derived a plasticity function that was virtually identical to that proposed in the BCM theory, if we assumed that variations in frequency were translated into variations in postsynaptic response during conditioning stimulation.

The missing piece was mechanism. Our initial hunch was that LTD is triggered by activation of the recently discovered mGluR (Bear 1988; Dudek & Bear 1989). Unfortunately, no good mGluR antagonists were available to test this hypothesis. However, we already had the NMDAR antagonist APV. We made an attempt, reasoning that it should at least shift the frequency–response function. We were utterly amazed to discover that APV blocked induction of LTD. Homosynaptic LTD, like LTP, was NMDAR-dependent! NMDARs were not 'switches', engaged only during Hebbian plasticity, as was commonly believed. Rather, they could function as analogue detectors of the degree of presynaptic and postsynaptic correlation.

We also had an early indication that there might be more to the LTD story in CA1. We consistently found that LTD magnitude increased substantially in slices that were maintained *in vitro* for more than 5–6 h. This LTD caused concern, however, because it could only be partly blocked by APV. In the laboratory, this became known as the 'late-in-the-day effect', and for years we were very mindful to avoid it in our experiments. We now know that the late-in-the-day effect reflects the added contribution of a second form of LTD that is mGluR- and protein-synthesis-dependent (Huber *et al.* 2000). The delayed expression of this LTD *in vitro* remains a mystery, but we believe it reflects the time it takes for protein synthesis to recover from the trauma of slice preparation.

Our findings on NMDAR-dependent LTD were debuted at the Society for Neuroscience Meeting in 1991. I was anxious about how they might be received, as I was a newcomer to the field of hippocampal synaptic plasticity. I gave a preview of the poster to Rob Malenka—a close friend, my roommate for the meeting, and one of the outstanding young hippocampal slice physiologists. His enthusiastic reaction convinced me that we were ready for prime time. We came home and submitted our paper for publication.

5. COMMON FORMS OF SYNAPTIC PLASTICITY IN HIPPOCAMPUS AND NEOCORTEX

Serena and I advanced as far as we could with field potential experiments, subsequently showing that CA1 LTD was saturable, reversible, the functional inverse of LTP and age-dependent (Dudek & Bear 1992, 1993). I considered that the next crucial issue was to determine if synapses in our model of receptive field plasticity, the visual cortex, behave like those in CA1. Fortunately, by this time Alfredo Kirkwood had discovered how to reliably elicit LTP in layer III of the visual cortex. We went on to demonstrate that visual cortical LTP is Hebbian, that LTP and LTD could be reliably elicited with high- and low-frequency stimulation, respectively, and that both forms of synaptic plasticity are NMDAR-dependent (Kirkwood *et al.* 1993; Kirkwood & Bear 1994*a*,*b*). Thus, it appeared that insights gained by the study of CA1 could indeed be applied to the visual cortex and the problem of receptive field plasticity.

Subsequent work from several laboratories, in species ranging from mice to humans, revealed that very similar principles guide synaptic plasticity in widely different regions of the cerebral cortex. As Leon Cooper had originally proposed, active synapses can be bidirectionally modified as a function of postsynaptic voltage. This plasticity occurs because voltage provides graded control of the NMDAR-dependent changes in postsynaptic Ca^{2+} that trigger LTD or LTP (figure 1). In a colloquium paper I suggested we refer to bidirectionally modifiable synapses with these properties as 'Cooper synapses' for obvious reasons (Bear 1996). I remember Eric Kandel remarking at the time that he did not think the name would catch on. He was right.

6. METAPLASTICITY AND THE SLIDING MODIFICATION THRESHOLD

Our characterization of bidirectional synaptic plasticity in layer III of the visual cortex had finally put us in a position to test the next key assumption of the BCM theory: the sliding modification threshold. If this idea is correct, reducing average visual cortical activity by a period of binocular deprivation should alter the properties of synaptic plasticity, favouring LTP over LTD. We confirmed this

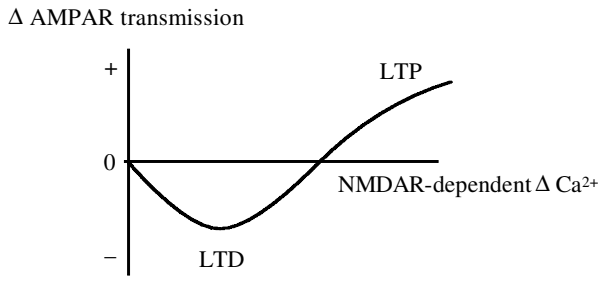

Figure 1. Function that governs the bidirectional modification of synaptic transmission mediated by AMPARs at glutamatergic synapses in area CA1 of the hippocampus and the superficial layers of the neocortex.

prediction, showing that binocular deprivation shifts the LTP threshold to lower stimulation frequencies, and that this can be reversed by restoring normal vision (Kirkwood *et al.* 1996). Thus, all the key assumptions of the BCM theory had now been validated: (i) active synapses are bidirectionally modifiable; (ii) the sign or polarity of the modification (LTD or LTP) depends on the level of postsynaptic response relative to a modification threshold; and (iii) the value of the modification threshold varies with the history of cortical activity.

The sliding threshold of the BCM theory is an example of what Cliff Abraham and I called *metaplasticity*, the plasticity of synaptic plasticity (Abraham & Bear 1996). There is now abundant evidence from several systems that the properties of synaptic plasticity depend importantly on the recent history of synaptic or cellular activity. In the visual cortex, we have identified an attractive mechanism for the sliding threshold, based on experience-dependent alterations in NMDARs. Ben Philpot has recently shown that unitary NMDAR-mediated EPSCs are slowed after a period of binocular deprivation, and that restoring normal vision rapidly reverses this change. These relatively small changes in kinetics have a large impact on EPSC summation (and therefore Ca^{2+} entry) at different stimulation frequencies (Philpot *et al.* 2001). Ben and Betsy Quinlan further found that the changes in NMDAR properties are probably explained by alterations in the subunit composition of synaptically expressed receptors. Receptors containing the NR2A subunit are delivered to synapses by visual experience, and are replaced by NR2B-containing receptors after a period of binocular deprivation (Quinlan *et al.* 1999*a*,*b*; figure 2). These changes in subunit composition alter the affinity of the receptor for glutamate (we made a good guess in 1987); however, it remains to be determined if the modifications of EPSC duration are alone responsible for the observed metaplasticity in the visual cortex. This question is now being examined using mice in which NMDARs have been genetically modified.

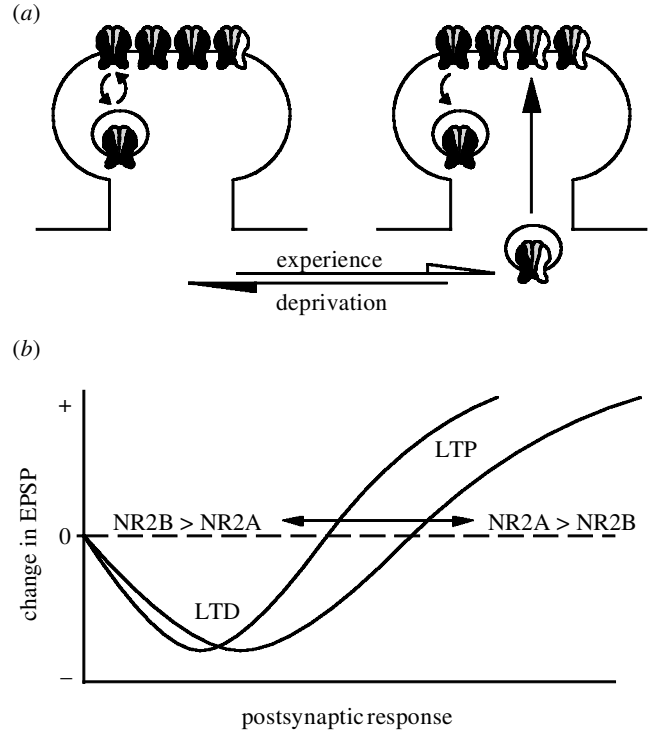

Figure 2. NMDAR regulation provides a molecular basis for a sliding synaptic modification threshold in visual cortex. (*a*) In the absence of visual experience, high constituitive expression of NR2B (black subunits) and reduced expression of NR2A (white subunits) leads to an increase in NR1/NR2B diheteromeric NMDARs at the synapse, and slower NMDAR-mediated EPSCs. Visual experience triggers increased NR2A expression and the rapid delivery of NR1/NR2A/NR2B triheteromeric receptors to the synapse, compensated by a net loss of surface NR1/NR2B diheteromers. (*b*) Model relating NMDAR subunit regulation to the properties of synaptic modification. The *y*-axis represents the lasting change in synaptic strength following conditioning stimulation at different levels of integrated postsynaptic response (*x*-axis). The curves are schematized from the data of Kirkwood *et al.* (1996). An increase in the NR2A/B ratio, as seen with light exposure after a period of dark-rearing, is proposed to be responsible for sliding the LTD–LTP crossover point (θ_m) to the right, thus decreasing the likelihood that synaptic strengthening will occur. Conversely, a fall in the NR2A/B ratio, as seen with binocular deprivation, slides θ_m to the left, favouring LTP over LTD. According to this model, the properties of synaptic modification depend upon the history of cortical activity, as originally proposed in the BCM theory, because of the activity-dependent expression of NR2A-containing NMDARs at cortical synapses. (Figure adapted from Philpot *et al.* (2001).)

7. ALTERED AMPAR FUNCTION DURING LTD

One of the things that made the discovery of LTD in the hippocampus exciting is that it appeared to be the mirror image of LTP, at least for AMPAR-mediated transmission. Thus, the study of LTD potentially offered a new way to address some of the sticky issues of the day, such as the site of LTP expression. At the time that LTD was discovered, it was believed that postsynaptic calcium/calmodulin-dependent protein kinase II (CaMKII) activity was essential for LTP induction. Inspired by a proposal from John Lisman (1989), Rob Malenka went on to show that LTD induction requires activation of a postsynaptic phosphatase cascade (Mulkey *et al.* 1994). These findings suggested that synaptic strength is bidirectionally regulated by the phosphorylation state of a set of postsynaptic proteins. The phosphoprotein of greatest interest was the postsynaptic AMPAR (Bear & Malenka 1994).

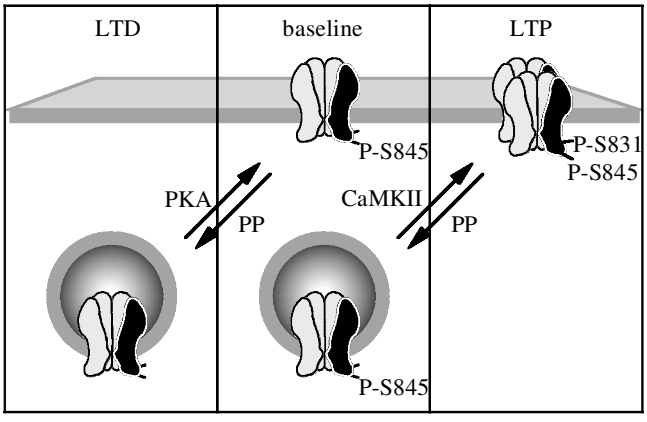

Figure 3. Model of bidirectional modifications of AMPAR phosphorylation and surface expression during LTD and LTP. In the basal state, ser-845 of the GluR1 subunit (shaded black) is phosphorylated. Induction of LTD leads to dephosphorylation of ser-845 by protein phosphastases (PP) and the internalization of AMPARs. These changes can be reversed by activating PKA. By contrast, induction of LTP from the basal state alters phosphorylation of the CaMKII site on GluR1, ser-831. CaMKII activation also leads to the delivery of AMPARs to the surface.

This set the stage for a memorable meeting I had with Rick Huganir during a visit to Johns Hopkins University in 1993. His laboratory had characterized multiple phosphorylation sites on the GluR1 subunit of AMPARs, and they were developing phosphorylation site-specific antibodies. He ushered me into his office, closed the door and started pressing me for information on how he might pharmacologically induce LTP in hippocampal slices. His idea was to induce LTP at a large population of synapses, and then use the phosphorylation site-specific antibodies to detect changes in receptor phosphorylation. I offered my opinion that this approach would be difficult, because LTP seems to require brief increases in postsynaptic Ca^{2+} that are difficult to achieve with bath applied drugs. A few days later, however, it suddenly occurred to me that LTD, which was induced by prolonged stimulation of NMDARs, might be more amenable to this approach. Hey-Kyoung Lee accepted the challenge, and was able to demonstrate that brief bath application of NMDA can induce LTD at a large population of CA1 synapses.

We went on to show that GluR1 was indeed dephosphorylated after induction of LTD. To our surprise, however, it was not the CaMKII site (ser-831) on GluR1 that was altered, but the PKA site (ser-845) instead (Lee *et al.* 1998). In subsequent experiments, we demonstrated that synaptically induced LTD and LTD reversal (dedepression) are induced by dephosphorylation and phosphorylation, respectively, of postsynaptic PKA substrates (Kameyama *et al.* 1998; Lee *et al.* 2000). These findings contrast with LTP and depotentiation, which are associated with bidirectional regulation of the CaMKII site on GluR1 (Barria *et al.* 1997; Lee *et al.* 2000). LTD and LTP are not, therefore, mirror symmetric (figure 3).

More recently, studies performed on hippocampal neurons in culture have revealed that AMPARs dephosphorylated at GluR1 ser-845 are rapidly internalized in response to NMDAR activation (Ehlers 2000). As in LTD, this change can be mimicked by inhibiting, and reversed by activating, PKA. Current opinion is that a reduction in the number of postsynaptic AMPARs is likely to be the major expression mechanism for LTD (Malinow & Malenka 2002). Consistent with this notion, Arnie Heynen and Betsy Quinlan showed that a redistribution of synaptic AMPAR protein occurs after induction of LTD in CA1 of adult rats *in vivo* (Heynen *et al.* 2000). These findings are important because they demonstrate that LTD has a molecular fingerprint that can be detected *in vivo*. As will be discussed, this information can be used to determine if naturally occurring synaptic modifications use the same mechanism.

8. IS LONG-TERM DEPRESSION A SUBSTRATE FOR RECEPTIVE FIELD PLASTICITY IN VISUAL CORTEX?

The BCM theory, devised to account for receptive field plasticity in the visual cortex, has obviously been very influential by pointing us in directions we might not have explored otherwise. In addition to being a guiding light, a theory can serve as a bridge to connect the molecular mechanisms of synaptic plasticity with their functional consequences. Implementing the BCM theory in neural network models shows that the mechanisms of LTP, LTD and metaplasticity *can* account for receptive field plasticity. However, the difficult experimental question remains, *do they*?

In 1997, a group of experts gathered at a Dahlem conference in Berlin to debate what formal criteria must be met to conclude that LTP is a substrate for learning. Simply stated, it was decided that: (i) learning must induce LTP; and (ii) induction of LTP must produce learning. Obviously this group was not concerned with the practicalities of achieving these standards. Satisfying them requires that we be able to measure and induce LTP in the selected population (which could be large and widely dispersed) of synapses that are modified during learning. A third criterion, that *the mechanism of* LTP *must be necessary for learning*, is more easily achieved. However, it is based on the assumption that LTP might be the *only* mechanism for a particular type of learning. Finding that learning survives the deletion of LTP would not be grounds for rejecting the hypothesis that LTP is a substrate for learning (Carew *et al.* 1998).

We are tackling a conceptually similar problem in the visual cortex. Is LTD a substrate for receptive field plasticity? One of the interesting predictions of the BCM theory is that the synaptic depression induced by monocular deprivation is not a consequence of retinal inactivity, as Stent assumed, but rather is caused by the residual 'noise' in the deprived eye. Cindi Rittenhouse confirmed this prediction by showing that inactivation of the retina with tetrodotoxin produces much less synaptic depression in the cortex than does simply closing the eyelid. Thus, deprivation-induced synaptic depression, like LTD, is homosynaptic (Rittenhouse *et al.* 1999). These findings then led us to wonder whether visual deprivation also triggers the same molecular changes as LTD. Remarkably, Arnie Heynen and Bongjune Yoon were able to show that 24 h of monocular deprivation during a sensitive period of postnatal life precisely mimics NMDAR-dependent LTD for altered phosphorylation and decreased neuronal

surface expression of AMPARs. Cheng-Hang Liu went on to find that the changes induced by monocular deprivation occlude the subsequent expression of homosynaptic LTD at synapses *ex vivo* (Heynen *et al.* 2002*a*). These findings demonstrate that *monocular deprivation induces LTD.*

The primary functional consequence of brief monocular deprivation is a reduction in visually evoked responses through the deprived eye. What are the functional consequences of inducing LTD? Arnie and Bongjune have recently found that prolonged low-frequency stimulation of the dorsal LGN, the thalamic relay of visual information, will induce NMDAR-dependent LTD of LGN-evoked field potentials and dephosphorylation of GluR1 ser-845 in primary visual cortex (Heynen *et al.* 2002*b*). We also found that *induction of LTD produces a reduction in visually evoked responses*, comparable to that caused by monocular deprivation.

Work is in progress to establish if the third Dahlem criterion will also be met, with the caveats already mentioned above. In the meantime, we can reconstruct, at least in part, the molecular chain of events that is set in motion by monocular deprivation in the visual cortex. The data support a model in which the activity in the deprived retina, relayed to the visual cortex by the LGN, weakly activates postsynaptic NMDARs. The activation is weak because it rarely correlates with responses evoked by visual stimulation of the open eye. Activated NMDARs admit Ca^{2+} ions into the postsynaptic neuron that, in turn, regulate a network of protein phosphatases and kinases. Among the consequences of the modest rise in intracellular calcium is dephosphorylation of postsynaptic PKA substrates, including ser-845 of the AMPAR GluR1 subunit, and the net loss of synaptic glutamate receptors. Consequently, the deprived eye no longer effectively drives synaptic excitation in the visual cortex.

9. CONCLUDING REMARK

None of the theories discussed here—those of Hebb, Stent and Cooper—provide a complete description of receptive field plasticity and information storage in the cerebral cortex (see Shouval *et al.* 2002). However, they all provided a framework that helped guide us towards the questions that are most relevant. Hebb's theory for a synaptic basis for memory in the cerebral cortex motivated the characterization of LTP by Bliss & Lømo (1973). The BCM theory motivated our characterization of LTD and the sliding modification threshold. These theories have been extraordinarily useful because they are simple enough for the consequences to be traced to assumptions, and concrete enough to be tested experimentally.

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GLOSSARY

AMPAR: α-amino-3-hydroxy-5-methylisoxazole-propionic acid receptor
APV: 2-amino-5-phosphonovaleric acid
BCM: Bienenstock–Cooper–Munro
EPSC: excitatory postsynaptic current
LGN: lateral geniculate nucleus
LTD: long-term depression
LTP: long-term potentiation
mGluR: metabotropic glutamate receptor
NMDA: *N*-methyl-D-aspartate
NMDAR: *N*-methyl-D-aspartate receptor
PKA: protein kinase A