Neuron, Vol. 44, 5–21, September 30, 2004, Copyright ©2004 by Cell Press

LTP and LTD: An Embarrassment of Riches

Review

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LTP and LTD, the long-term potentiation and depression of excitatory synaptic transmission, are widespread phenomena expressed at possibly every excitatory synapse in the mammalian brain. It is now clear that "LTP" and "LTD" are not unitary phenomena. Their mechanisms vary depending on the synapses and circuits in which they operate. Here we review those forms of LTP and LTD for which mechanisms have been most firmly established. Examples are provided that show how these mechanisms can contribute to experience-dependent modifications of brain function.

Exactly a decade ago, we wrote a review on NMDA receptor (NMDAR)-dependent LTP and LTD in the hippocampus (Bear and Malenka, 1994)—a review that updated the reader on the latest findings on the mechanisms of these two forms of synaptic plasticity. At the time, controversy was swirling around the issue of whether LTP was primarily due to pre- or postsynaptic modifications and whether nitric oxide was indeed a retrograde messenger triggering presynaptic changes during LTP. In addition, the existence of an experimentally reproducible form of LTD had just been established along with some of the mechanisms responsible for its triggering. It is pleasing to report that science has indeed progressed, and much has changed since 1994. Here we will attempt to highlight the progress that has been made over the ensuing 10 years in terms of our understanding of the underlying mechanisms of these and other major forms of long-lasting synaptic plasticity. We will also briefly discuss some advances in our understanding of the functional roles that LTP and LTD may play in specific types of experience-dependent plasticity.

While NMDAR-dependent LTP and LTD in the CA1 region of the hippocampus remain the most extensively studied and therefore prototypic forms of synaptic plasticity, it is now clear that there are additional forms of LTP and LTD which may share some, but certainly not all, of the properties and mechanisms of NMDAR-dependent LTP and LTD. Therefore, when discussing LTP and LTD it is now necessary to define at which specific synapses these phenomena are being studied, at what time point during development, and how they are being triggered (e.g., via NMDARs or metabotropic glutamate receptors [mGluRs]). Indeed, it may be most useful to conceptualize LTP and LTD as a general class of cellular/synaptic phenomena. Just as different neurons express different complements of ion channels to control their firing properties, neurons can vary in terms of the specific forms of LTP and LTD they express.

We would also argue that it is no longer particularly productive to debate the generic question of whether LTP and LTD are cellular/synaptic mechanisms for memory. LTP and LTD are experimental phenomena, which can be used to demonstrate the repertoire of long-lasting modifications of which individual synapses are capable. It is a daunting task to demonstrate that identical synaptic modifications due to the same mechanisms underlying some form of LTP or LTD occur in vivo in response to experience. It is even more difficult to prove that these LTP or LTD-like modifications subserve essential functional roles. Nevertheless, given the ubiquity of various forms of LTP and LTD at excitatory synapses throughout the brain and the clear computational advantages they afford, it seems virtually certain that the brain takes advantage of the neuronal capability to express long-lasting activity-dependent synaptic modifications as at least one of the key mechanisms by which experiences modify neural circuit behavior.

Thus, questions about the functional roles of "LTP" or "LTD" must be placed into very specific contexts. It first must be determined which synapses and circuits mediate a specific type of experience-dependent plasticity. Then the types of LTP and LTD that can occur at those synapses must be defined. Finally, largely through correlational studies involving genetic and pharmacological manipulations, it is possible to begin to establish that in vivo experiences generate synaptic modifications analogous to LTP and LTD and these modifications are required for the behavioral or cognitive plasticity generated by the experience.

We believe that the mechanisms underlying the various forms of LTP and LTD, which can be elicited in the brain, subserve an enormous host of functions both during development and all forms of experience-dependent plasticity, including learning and memory. Thus it remains of great importance to continue to probe the detailed mechanisms underlying LTP and LTD (Malenka, 2003). However, it also should be noted that LTP and LTD are certainly not the only means by which the activity generated by experience can modify neural circuit behavior (for examples, see Abraham and Bear, 1996; Turrigiano and Nelson, 2004; Zhang and Linden, 2003). Given the importance of plastic changes in the brain for survival, neurons likely use every type of plasticity mechanism at their disposal, and thus there is likely great redundancy.

In this review we will attempt to concisely review some of the detailed mechanisms underlying some of the major forms of synaptic plasticity in the mammalian brain. We will then discuss two examples in which attempts have been made to examine whether synaptic modifications analogous to LTP or LTD actually occur in vivo in response to experience.

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NMDA Receptor-Dependent LTP

How does one review a topic on which performing a PubMed search yields over 6000 publications (using the term "long-term potentiation or LTP") and one on which innumerable reviews have already been written? We will accomplish this task by limiting our discussion to what we believe is reasonably well accepted about the mechanisms of NMDAR-dependent LTP in the CA1 region of the hippocampus and pointing out some of the key issues that need to be resolved. We begin our discussion by focusing on the so-called "early" phase of LTP—that component of LTP lasting 60 or so minutes—and then briefly mention the "late," protein synthesis-dependent component of LTP. Because of the vast literature on this topic, for citations we rely on a mixture of previous reviews and primary research papers.

LTP Induction

It is well established that, by definition, the NMDAR-dependent form of LTP requires synaptic activation of NMDARs during postsynaptic depolarization which, experimentally, can be achieved using any number of different induction protocols (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999). This leads to the influx of Ca^{2+} through the NMDAR channel and a rise in Ca^{2+} within the dendritic spine, an absolutely necessary trigger for LTP. Surprisingly, however, we still know little about the detailed properties of the spine Ca^{2+} signal that is required to trigger LTP. A rise in Ca^{2+} (Lynch et al., 1983; Malenka et al., 1988) lasting less than 2–3 s (Malenka et al., 1992) appears to be sufficient for LTP, but the magnitude and microdomain location of this signal is unknown. Are the critical Ca^{2+} sensors for triggering LTP right at the mouth of the NMDAR channel or does Ca^{2+} also need to diffuse further into the spine, perhaps to cause additional release of Ca^{2+} from intracellular stores (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999)? It also remains elusive whether activation of NMDARs alone is sufficient to elicit a stable form of LTP or rather that additional factors are necessary (Kauer et al., 1988; Malenka and Nicoll, 1993).

What intracellular signaling pathways are activated by NMDARs and are necessary for triggering LTP? Enormous effort by many labs has been devoted to this question, and as pointed out previously (Sanes and Lichtman, 1999), the resulting literature is very confusing at best. A contributing factor for this confusion may be that for many of the signaling molecules suggested to play a role in LTP, the appropriate experiments have not been performed to determine whether a particular protein is a mediator or modulator (Sanes and Lichtman, 1999). A mediator is a protein or factor, such as the NMDAR or Ca^{2+}, that under virtually all experimental conditions is required to generate LTP. A modulator is a factor that can alter LTP but is not essential for its occurrence. There are many ways to impair the generation of LTP, such as inhibiting transmitter release during the LTP induction protocol, inhibiting NMDAR function, or enhancing inhibition. Thus the finding that pharmacological or genetic manipulation of some protein affects LTP is not sufficient to conclude that the protein is a key and necessary component of the mechanisms underlying LTP; that is, a mediator rather than a modulator. Of course, classification of a protein as a mediator versus a modulator is not always clear-cut, but we think it is useful to keep this general distinction in mind when considering the mechanisms underlying LTP and LTD.

Another potential reason for the diversity of signaling proteins implicated in LTP is that there may be multiple intracellular cascades that are capable of inducing LTP. It now seems clear that during development the molecular mechanisms of LTP change (Esteban et al., 2003; Jensen et al., 2003; Kirkwood et al., 1997; Yasuda et al., 2003). Thus some caution is warranted before assuming that findings from dissociated cultured neurons or hippocampal slice cultures necessarily apply to synapses in more mature preparations. It also has been suggested that different LTP induction protocols may activate distinct signaling cascades that generate LTP with different expression mechanisms (Hoffman et al., 2002; Lisman, 2003; Minichiello et al., 2002). While this is an important possibility, the experimental evidence in support of this view is limited, and potentially key experiments that directly test this hypothesis have not been performed. For example, if LTP induced by high-frequency tetanic stimulation activates intracellular signaling and expression mechanisms not elicited by a pairing protocol (in which low-frequency afferent stimulation is paired with postsynaptic depolarization) (Lisman, 2003) then following saturation of LTP using a pairing protocol, it should be possible to generate additional LTP using tetanic stimulation. This experiment, however, has not been performed.

Given these caveats, what can we say about the intracellular cascades required to trigger LTP? It appears clear that calcium/calmodulin-dependent protein kinase II (CaMKII) is required as a mediator for NMDAR-dependent LTP, no matter how it is induced. The evidence in support of a requisite role for CaMKII in LTP is compelling and has been extensively reviewed elsewhere (Lisman et al., 2002; Malenka and Nicoll, 1999). The only exception to this conclusion is that, during early postnatal development, at a time point at which CaMKII expression is low, LTP does not require CaMKII activation (Kirkwood et al., 1997; Yasuda et al., 2003). Several other protein kinases have also been implicated in playing key roles in LTP (Lynch, 2004), although whether these are mediators or modulators remains to be determined. PKA, cAMP-dependent protein kinase, is required for LTP during early postnatal development (Yasuda et al., 2003) and later in development it may be important for indirectly, via phosphorylation of inhibitor 1, inhibiting protein phosphatase 1 activity and thus enhancing CaMKII autophosphorylation (Blitzer et al., 1998; Brown et al., 2000; Lisman, 1989). (Its potential role in later phases of LTP will be discussed below.) For many years, protein kinase C (PKC) has also been suggested to be important for LTP (Bliss and Collingridge, 1993; Hu et al., 1987; Linden and Routtenberg, 1989; Malenka and Nicoll, 1999; Malinow et al., 1989), in particular the atypical PKC isozyme, protein kinase M zeta (PKMζ) (Hrabetova and Sacktor, 1996; Ling et al., 2002). More recently, the mitogen-activated protein kinase (MAPK) cascade that activates extracellular signal-regulated kinases (ERKs) has been implicated in LTP as well as in some forms of learning and memory (Sweatt, 2004; Thomas and Huganir, 2004). Two other kinases deserving of mention are phosphatidylinositol 3-kinase (PI3 kinase) and the tyrosine kinase Src. PI3 kinase appears to be required

for a form of LTP that involves the trafficking of AMPARs to synapses in dissociated cultured hippocampal neurons (Man et al., 2003). Src, on the other hand, may serve to enhance NMDAR function during the LTP induction protocol (Salter and Kalia, 2004).

Clearly, except for the role of CaMKII, the signal transduction cascades required for triggering LTP remain a quagmire with many potential players but few definitive answers about the specific roles that any individual signaling molecule plays. This topic becomes even more complex when considering the possibility of retrograde messengers, which will be discussed in the next section. Given the incredible complexity and redundancy of intracellular signaling networks in all cell types (Bhalla and Iyengar, 1999; Neves and Iyengar, 2002), this situation may not be particularly surprising.

LTP Expression

The seemingly simple question of whether, initially, the increase in synaptic strength during LTP is due primarily to some postsynaptic modification in AMPARs or some presynaptic change in transmitter release generated a passionate debate that lasted for a decade. Strong arguments were made on both sides, with disagreements most often being about the reproducibility of experimental results (Kullmann and Siegelbaum, 1995; Malenka and Nicoll, 1999; Nicoll and Malenka, 1999). It now appears safe to state that a major mechanism for the expression of LTP involves increasing the number of AMPARs in the plasma membrane at synapses via activity-dependent changes in AMPAR trafficking (Bredt and Nicoll, 2003; Malenka and Nicoll, 1999; Malinow and Malenka, 2002; Song and Huganir, 2002). In addition, another component of LTP involves modification of the biophysical properties of AMPARs themselves via their direct phosphorylation (Benke et al., 1998; Lee et al., 2003; Malenka and Nicoll, 1999; Soderling and Derkach, 2000). Current understanding of the detailed molecular mechanisms that control the activity-dependent regulation of AMPAR trafficking to synapses has been reviewed extensively elsewhere (Bredt and Nicoll, 2003; Malinow and Malenka, 2002; Song and Huganir, 2002). Suffice it to say that it appears clear that CaMKII and the AMPAR subunit GluR1 play particularly important roles (Hayashi et al., 2000; Zamanillo et al., 1999) but that many molecular details remain to be worked out. For example, the key substrates for CaMKII must include as yet unidentified proteins in addition to GluR1 (Hayashi et al., 2000; Lee et al., 2003). Furthermore, the source of the AMPARs that are delivered to synapses during LTP is unknown as are the detailed molecular interactions that deliver and retain the AMPARs in the postsynaptic density. While specific hypotheses have been offered (Malinow et al., 2000; Sheng and Hyoung Lee, 2003), there are some discrepancies between the findings obtained from studies that involve overexpression of recombinant proteins versus those that genetically remove the same proteins. Nonetheless, molecular knowledge of the steps controlling AMPAR trafficking is advancing rapidly, and such information will certainly be important for providing additional means to probe the functions and perhaps even the therapeutic potential of LTP.

The idea that presynaptic changes also contribute to NMDAR-dependent LTP certainly is not dead (Choi et al., 2000; Emptage et al., 2003; Zakharenko et al., 2003). However, as this form of LTP is triggered postsynaptically, any relatively rapid presynaptic modifications must involve a retrograde messenger that communicates from the postsynaptic cell back to the presynaptic terminals, and the identity of any such messenger remains elusive. Popular candidates of the past, such as nitric oxide and arachidonic acid (Williams et al., 1993), have largely fallen by the wayside and no longer receive significant attention. Neurotrophins such as BDNF have also been proposed to play this role (Poo, 2001), but there is evidence that a role for BDNF in LTP involves its release from presynaptic, not postsynaptic, sources (Zakharenko et al., 2003). Prime additional candidates for synaptic retrograde messengers during LTP include the large number of synaptic cell adhesion molecules, which physically connect and align the presynaptic transmitter release apparatus with the postsynaptic density (Sudhof, 2001).

Maintaining LTP

While much of the work on NMDAR-dependent LTP has focused on the mechanisms responsible for the initial increase in synaptic strength lasting 30–60 min, arguably of greater interest and importance are the mechanisms that allow LTP to last hours, days, or even weeks. It is well established that, like all long-lasting cell biological phenomena, the so-called "late phases" or longer-lasting components of LTP require new protein synthesis and gene transcription (Abraham and Williams, 2003; Lynch, 2004; Pittenger and Kandel, 2003). Signaling molecules that are thought to link the activity that induces LTP to the nucleus include PKA, CaMKIV, and MAPK, which in turn activate the key transcription factor CREB as well as immediate early genes such as zif268 (Abraham and Williams, 2003; Lynch, 2004; Pittenger and Kandel, 2003; Silva et al., 1998). An intriguing hypothesis is that, during the synaptic activation to induce LTP, a "synaptic tag" is generated that functions to capture or sequester plasticity-related proteins, which in turn are required to stabilize the initial increase in synaptic strength (Frey and Morris, 1998). However, essentially nothing is known about the identity of the synaptic tag or the newly synthesized proteins that are required to maintain LTP.

An obvious possibility for the longer-term maintenance of LTP that has received significant attention is that synapses at which LTP has occurred undergo structural remodeling which locks-in the synaptic weight changes. Morphological changes that have been reported to accompany LTP include growth of new dendritic spines, enlargement of preexisting spines and their associated postsynaptic densities (PSDs), and the splitting of single PSDs and spines into two functional synapses (Abraham and Williams, 2003; Yuste and Bonhoeffer, 2001). Recently, an elegant study in which single spines were activated using photolysis of caged glutamate and imaged with two-photon microscopy directly demonstrated that LTP was accompanied by enlargement of dendritic spines (Matsuzaki et al., 2004). Interestingly, this increase in spine size was only transient in large, presumably more mature, mushroom-shaped spines but was persistent in smaller spines. A key element in any structural alterations in dendritic spines is the actin cytoskeleton, which is greatly enriched in

spines (Matus, 2000). Consistent with a role for actin cytoskeletal reorganization in maintaining LTP, inhibitors of actin polymerization impair LTP (Kim and Lisman, 1999; Krucker et al., 2000). Furthermore, LTP in vivo is accompanied by a long-lasting increase in F-actin content within spines, an increase that appears to involve inhibition of actin depolymerization (Fukazawa et al., 2003).

The molecular mechanisms controlling the generation and maturation of spines have received significant attention recently, and it has been found that overexpression in dissociated cultured neurons of a number of different proteins, which are components or regulators of the postsynaptic molecular scaffold, cause increases in spine size (Hering and Sheng, 2001). In terms of LTP, a particularly attractive model is that initially LTP involves the insertion of AMPARs and associated molecules into the PSD and this leads to the growth of the PSD/spine (Lisman and Zhabotinsky, 2001; Lüscher et al., 2000). Simultaneously or soon thereafter, there is likely a concomitant increase in the presynaptic active zone, the size of which always closely matches that of the PSD (Lisman and Harris, 1993). Thus, according to this model, LTP involves an increase in synaptic strength accompanied by the physical growth of the synapse. An intriguing possibility is that, in addition to the delivery of AMPARs to synapses, LTP involves the addition of "slot proteins" that act as placeholders for AMPARs at the synapse (Malinow and Malenka, 2002; Shi et al., 2001) and which contribute to synaptic growth. Dendritic synthesis of key proteins such as αCaMKII or AMPAR subunits may also play a key role in structural modifications during LTP (Ju et al., 2004; Steward and Schuman, 2001).

Mossy Fiber LTP: A cAMP-Dependent Presynaptic Form of Plasticity

Although NMDAR-dependent LTP has received the lion's share of attention over the last two decades, it is clear that another, mechanistically distinct form of LTP coexists in the hippocampus at mossy fiber synapses—the synapses between the axons of dentate gyrus granule cells (i.e., mossy fibers) and the proximal apical dendrites of CA3 pyramidal cells (Nicoll and Malenka, 1995). This mossy fiber LTP has received increased attention in part because mechanistically similar forms of LTP have also been observed at corticothalamic synapses (Castro-Alamancos and Calcagnotto, 1999) and cerebellar parallel fiber synapses (Linden, 1997; Salin et al., 1996), raising the possibility that, like NMDAR-dependent LTP, mossy fiber LTP plays multiple functional roles.

Unlike NMDAR-dependent LTP, the triggering of mossy fiber LTP does not require activation of NMDARs (Harris and Cotman, 1986; Nicoll and Malenka, 1995; Zalutsky and Nicoll, 1990) or for that matter other ionotropic glutamate receptors (Castillo et al., 1994). It remains, however, controversial whether mossy fiber LTP does not require any postsynaptic activation and is triggered solely by an activity-dependent rise in intracellular calcium concentration in presynaptic terminals (Castillo et al., 1994; Mellor and Nicoll, 2001; Nicoll and Malenka, 1995; Zalutsky and Nicoll, 1990) or also can be triggered by postsynaptic calcium increases mediated by a number of different sources (Henze et al., 2000; Yeckel et al., 1999). It does seem apparent that activation of presynaptic kainate receptors by endogenous glutamate plays an important facilitatory role in triggering mossy fiber LTP (Contractor et al., 2001; Lauri et al., 2001, 2003; Schmitz et al., 2003).

Pharmacological and genetic manipulations suggest that a rise in presynaptic calcium induces mossy fiber LTP, at least in part by activation of calcium-stimulated adenylyl cyclases and the consequent activation of PKA (Nicoll and Malenka, 1995; Villacres et al., 1998; Wang et al., 2003). Since there is compelling and widely accepted evidence that the expression of mossy fiber LTP involves a presynaptic increase in glutamate release (Kawamura et al., 2004; Linden, 1997; Reid et al., 2004; Tong et al., 1996; Weisskopf and Nicoll, 1995; Zalutsky and Nicoll, 1990), research has focused on identifying presynaptic PKA substrates that play a critical role. As presynaptic terminals are relatively inaccessible to the sort of intracellular, postsynaptic manipulations that have proved invaluable in examining NMDAR-dependent LTP, a major approach to mossy fiber LTP has been examination of knockout mice lacking specific presynaptic proteins. Initially, the prime presynaptic candidates for playing a role in mossy fiber LTP were synapsins I and II, which are robustly phosphorylated by PKA (Sudhof et al., 1989). However, normal mossy fiber LTP was elicited in mice lacking these proteins (Spillane et al., 1995). In contrast, mossy fiber LTP is absent in mice lacking the synaptic vesicle protein Rab3A (Castillo et al., 1997), which binds to two different PKA substrates, the synaptic vesicle-associated rabphilin and the major active zone constituent RIM1α (Sudhof, 2004). Knockout mice lacking rabphilin exhibited normal mossy fiber LTP (Schlüter et al., 1999), whereas mossy fiber LTP was absent in mice lacking RIM1α (Castillo et al., 2002). Thus, mossy fiber LTP appears to require the interaction of Rab3A and RIM1α, proteins that function at the interface of synaptic vesicles and the active zone. Consistent with this hypothesis, LTP at the synapses between cultured cerebellar granule cells and Purkinje neurons is absent when the source of the neurons are RIM1α knockout mice (Lonart et al., 2003). This LTP can be rescued by presynaptic expression of wild-type RIM1α but not by a mutant RIM1α in which a specific residue, serine 413, has been mutated to prevent its phosphorylation by PKA (Lonart et al., 2003). Clearly, it will be important to test the role of phosphorylation of RIM1α serine 413 in mossy fiber LTP in more intact preparations as well as how this phosphorylation alters its interactions with other proteins.

Although the genetic evidence for a critical role of Rab3A and RIM1α in mossy fiber LTP is strong, these results do not rule out roles for additional molecules. If mossy fiber LTP in fact can be triggered postsynaptically, retrograde communication must occur to cause the presynaptic increases in transmitter release. Intriguing candidates for such signaling are *trans*-synaptic interactions between postsynaptic EphB receptors and presynaptic B-ephrins (Contractor et al., 2002). In terms of additional presynaptic expression mechanisms, evidence has been presented that a PKA-dependent modulation of I_h channels occurs during mossy fiber LTP and

this causes depolarization of presynaptic terminal (Mellor et al., 2002). However, neither presynaptic resting calcium levels (Regehr and Tank, 1991) nor action potential-evoked presynaptic calcium entry (Kamiya et al., 2002) are detectably enhanced during mossy fiber LTP. Furthermore, subsequent work questioned the specificity of the agents used to block I_h channels and demonstrated that neither mossy fiber LTP nor LTP at parallel fiber-Purkinje cell synapses was affected by blockade of I_h channels (Chevaleyre and Castillo, 2002). Other suggested mediators or modulators of mossy fiber LTP include the pituitary adenylate cyclase activating polypeptide type 1 receptor (Otto et al., 2001) and zinc, which is coreleased with glutamate from mossy fiber terminals (Li et al., 2001).

In summary, mossy fiber LTP appears to involve a PKA-dependent, long-lasting modulation of the presynaptic release machinery leading to an increased probability of transmitter release as well as perhaps the recruitment of new or previously silent release sites (Reid et al., 2004; Tong et al., 1996). Rab3A and RIM1α play critical roles in this process, but much remains unknown about how they are modulated by PKA and perhaps other intracellular signaling cascades. Furthermore, the mechanisms that mediate the long-lasting maintenance of this form of LTP are unclear. Like NMDAR-dependent LTP, new protein synthesis appears to be required for maintaining mossy fiber LTP (Calixto et al., 2003; Huang et al., 1994). However, it remains unknown whether the increase in PKA activity following the induction of mossy fiber LTP is maintained for tens of minutes or hours. We also do not know whether long-lasting structural changes occur at the synapses that express mossy fiber LTP. The answers to these sorts of questions will certainly facilitate our understanding of not only the mechanisms that underlie this prevalent form of synaptic plasticity but also its functional roles.

NMDA Receptor-Dependent LTD

Back in 1994, it was a relatively simple matter to review LTD. At that time, studies of LTD in the forebrain were in their infancy. Although it was known that LTP could be disrupted and reversed by synaptic activity, a phenomenon termed "depotentiation" (Barrionuevo et al., 1980; Fujii et al., 1991; Staubli and Lynch, 1990), a key breakthrough in 1992 was the establishment of stimulation protocols that could reliably elicit homosynaptic LTD of basal synaptic responses at Schaffer collateral synapses in the CA1 region of hippocampal slices (Dudek and Bear, 1992). It was quickly established that this form of LTD induced by low-frequency stimulation (LFS: 0.5–3 Hz) required activation of NMDARs (Dudek and Bear, 1992; Mulkey and Malenka, 1992), a rise in postsynaptic calcium ion concentration (Mulkey and Malenka, 1992), and activation of a serine-threonine protein phosphatase cascade (Mulkey et al., 1994; Mulkey et al., 1993; Mulkey and Malenka, 1992) and that LTD with identical properties could be observed in the neocortex of several species (Kirkwood and Bear, 1994; Kirkwood et al., 1993). The latter finding was encouraging, because it suggested that mechanistic studies in the experimentally tractable hippocampal slice would yield insights that are broadly applicable to excitatory synapses at many locations in the forebrain.

What a difference a decade makes. Ten years and over 750 papers later, it is now clear that LTD is indeed very widely expressed, quite possibly at all the excitatory synapses in the CNS. But it is also clear that there is a rich diversity of mechanisms and that caution is warranted when generalizing from one synapse to another. LTD remains a compelling phenomenon to study, as evidence now suggests that the mechanisms contribute to experience-dependent development, learning and memory, addiction, and neurological disorders such as mental retardation and Alzheimer's disease.

We have chosen to focus mainly on LTD in area CA1, with only a brief discussion of some interesting variations. This seems justified, as it is the prototypical form of LTD in the forebrain and its mechanistic understanding is probably most advanced. However, even narrowing the literature search to area CA1 yields several hundred papers published since the model was established. We begin with a discussion of LTD triggered by NMDAR activation. A second type of LTD triggered by activation of mGluRs is described later in the review.

LTD Induction

The typical protocol for inducing LTD involves prolonged repetitive synaptic stimulation at 0.5–5 Hz. A robust change usually requires many stimuli (e.g., 900) (Dudek and Bear, 1992, 1993), although this number can be reduced if the postsynaptic neuron is modestly depolarized to relieve the Mg^{2+} block of the NMDAR (Selig et al., 1995) or if specific neuromodulators are applied (Kirkwood et al., 1999; Scheiderer et al., 2004). The optimal protocol also appears to depend on the age of the animal; in adults, repeated delivery of paired pulses at 1 Hz for 900 s appears to be particularly effective (Kemp et al., 2000; Lee et al., 2003; Thiels et al., 1996), although this protocol can also induce mGluR-dependent LTD, as discussed below. In considering the question of optimal induction protocols, it is important to recognize that induction of LTD (as well as LTP) by a particular type of stimulation is influenced by the recent history of synaptic or cellular activity (Abraham and Bear, 1996; Ngezahayo et al., 2000). In fact, there is evidence that, during LFS, activity early in the stimulus train activates metaplasticity that is permissive for LTD induction by stimuli late in the train (Mizuno et al., 2001; Mockett et al., 2002). Although this is far less of an issue today than it was 10 years ago, it is our opinion that laboratories that still fail to find LTD in the hippocampus simply have not found the optimal stimulation protocol for their experimental conditions.

Inhibition of NMDARs blocks LTD (Dudek and Bear, 1992; Mulkey and Malenka, 1992), and activation of NMDARs induces it (Cummings et al., 1996; Kamal et al., 1999; Kandler et al., 1998; Lee et al., 1998; Li et al., 2004). NMDARs admit Ca^{2+} into the postsynaptic neuron, and buffering a rise in [Ca^{2+}] prevents LTD (Mulkey and Malenka, 1992). Moreover, photolytic intracellular uncaging of Ca^{2+} induces LTD (Yang et al., 1999). Thus, the simple model emerged that Ca^{2+} entering the postsynaptic dendritic spine through the NMDAR is the trigger for LTD. Like LTP, however, the quantitative characteristics of the postsynaptic Ca^{2+} signal that is required to trigger LTD remain to be determined. In addition, recent data suggest that a revision might be

required that takes into account the subtype of NMDAR that is activated and alternate sources of Ca^{2+}.

An early indication that not all NMDARs are equivalent was that antagonists with different affinities for NR2A/B and NR2C/D subunits differentially affect LTD relative to LTP (Hrabetova et al., 2000). Recent studies have attempted to discriminate between the involvement of NR2A- and NR2B-containing receptors in triggering LTD, but the data are contradictory (Hendricson et al., 2002; Liu et al., 2004; Tang et al., 1999). Different NR2 subunits confer distinct channel properties (Monyer et al., 1992) and recruit different intracellular signaling molecules (Leonard et al., 1999). Getting to the bottom of how NMDAR subunit composition regulates induction of LTD (and LTP) will require experiments that can discriminate between such overt and covert differences. However, it remains a very important question, because NMDAR subunit composition at synapses is regulated by activity (Barria and Malinow, 2002; Quinlan et al., 1999; Williams et al., 1998, 2003) and this is likely to control the propensity for LTD over LTP.

In addition to Ca^{2+} entering through NMDARs, a role for Ca^{2+} release from intracellular stores has been proposed for LTD. Interestingly, intracellular Ca^{2+} stores appear to contribute little to LTD when NMDARs are activated optimally but have an important role during suboptimal stimulation protocols (Nakano et al., 2004). However, release of Ca^{2+} from intracellular stores can cause the spread of LTD to neighboring, unstimulated synapses (Nishiyama et al., 2000). This heterosynaptic LTD apparently is held in check normally by PKC and PI3 kinase activity (Daw et al., 2002) via an unknown mechanism.

A seemingly well-accepted finding is that LTD is prevented by postsynaptic introduction of protein phosphatase inhibitors that primarily target calcineurin or protein phosphatase 1 (PP1) (Kirkwood and Bear, 1994; Mulkey et al., 1993, 1994), and biochemical studies have indicated that LTD is correlated with dephosphorylation of postsynaptic PKC and PKA substrates without a detectable change in CaMKII substrate phosphorylation (Hrabetova and Sacktor, 2001; Kameyama et al., 1998; Lee et al., 1998; van Dam et al., 2002). There is a particularly strong case to be made for dephosphorylation of PKA substrates as a trigger for LTD. Postsynaptic inhibition of PKA, or displacement of it from intracellular anchoring proteins, causes a run-down of synaptic transmission that occludes LTD. Moreover, postsynaptic activation of PKA can reverse previously established LTD without affecting baseline transmission (Kameyama et al., 1998). The question remains as to how induction of LTD selectively dephosphorylates synaptic PKA substrates without affecting CaMKII substrate phosphorylation. One possibility is that there is a very precise recruitment of protein phosphatases, in particular PP1, to selected substrates via binding to specific synaptic targeting proteins (Morishita et al., 2001). Indeed, like CaMKII (Lisman et al., 2002; Shen and Meyer, 1999), NMDAR activation can alter the subcellular distribution of PP1 and recruit it to synapses (Morishita et al., 2001). Additionally, there may be a selective loss or translocation of PKA at the synapse (Gomez et al., 2002).

LTD Expression and Maintenance

At the time of our 1994 review, a reasonable conjecture was that LTP and LTD are expressed as a consequence of bidirectional changes in postsynaptic AMPAR phosphorylation. Subsequent research focused on changes in phosphorylation of the C-tail of the GluR1 subunit. LTP was found to be associated with phosphorylation of ser-831, a substrate of CaMKII and PKC, without a change in ser-845, a PKA substrate (Barria et al., 1997; Lee et al., 2000). Conversely, LTD was found to be associated with selective dephosphorylation of ser-845, without any change in ser-831 (Lee et al., 1998, 2000). Dephosphorylation of ser-845 is likely to be partially responsible for expression of LTD, because it decreases the AMPAR open channel probability (Banke et al., 2000). Indeed, mice with a "knockin" alanine substitution for serines 845 and 831 lack NMDAR-dependent LTD in area CA1 (Lee et al., 2003).

There is much more to LTD expression, however, than posttranslational modification of AMPAR channels: changes in phosphorylation also are accompanied by a physical loss of AMPARs at the synapse. It has been established in a number of hippocampal preparations that AMPARs are rapidly internalized in response to LTD-inducing stimuli via a dynamin- and clathrin-dependent mechanism. (Beattie et al., 2000; Carroll et al., 1999; Ehlers, 2000; Heynen et al., 2000; Lee et al., 2002; Lin et al., 2000; Luthi et al., 1999; Man et al., 2000). Furthermore, internalized receptors appear to be dephosphorylated at GluR1 ser-845 (Ehlers, 2000).

Precisely how Ca^{2+}-dependent phosphatase activity rapidly reduces surface expression of AMPARs still remains uncertain, but there is evidence that it depends on interactions of the intracellular, C-terminal tails of AMPAR subunits with proteins that variously tether or direct them to compartments inside the neuron, the extrasynaptic surface membrane, or the synapse. Calcineurin, by dephosphorylating key components of the endocytic machinery, may also directly enhance endocytosis (Lai et al., 1999; Slepnev et al., 1998). The field of activity-dependent AMPAR trafficking has been the subject of several recent reviews, and the reader again is directed to them for more detailed information (Bredt and Nicoll, 2003; Carroll et al., 2001; Malinow and Malenka, 2002; Sheng and Hyoung Lee, 2003; Song and Huganir, 2002). Suffice it to say that a number of converging lines of evidence point to the AMPAR GluR2 subunit as a key regulator of the AMPAR endocytosis that initiates LTD. In response to NMDAR activation, the clathrin adaptor protein complex AP2 apparently is recruited to a membrane-proximal region of the GluR2 C-tail where it initiates clathrin coat assembly and receptor endocytosis (Lee et al., 2002). Peptides that selectively prevent this interaction prevent LFS-induced LTD. Association of the more distal tail of GluR2 with the PDZ domain-containing proteins GRIP and PICK1 appear to be important for LTD, but exactly how remains the subject of debate (Daw et al., 2000; Kim et al., 2001; Seidenman et al., 2003; Terashima et al., 2004). Furthermore, it remains unclear how the disruption of GluR1 phosphorylation prevents LTD (Lee et al., 2003); what accounts for the parallel changes in synaptic expression of GluR1 and GluR2 during LTD (Heynen et al., 2000); how dephosphorylation of postsynaptic PKA substrates

induces or maintains LTD (Kameyama et al., 1998); and how LTD survives genetic ablation of both GluR2 and GluR3 subunits (Meng et al., 2003).

If LTD is indeed a result of a reduced steady-state number of AMPARs, then the question of LTD maintenance (like LTP) merges with the general issue of how stable numbers of synaptic AMPARs are maintained especially in face of the fact that some population of AMPARs appear to cycle rapidly into and out of the synaptic membrane (Lüscher et al., 1999; Nishimune et al., 1998; Shi et al., 2001; Song et al., 1998). For transmission to remain constant in the face of this turnover, as mentioned above, it has been suggested that there must exist "slot proteins" that act as place holders for AMPARs at the synapse (Malinow and Malenka, 2002; Shi et al., 2001). While recruitment of more slot proteins could lead to LTP, LTD could result from a net loss of slot proteins and their complement of postsynaptic AMPARs. Thus, identifying slot proteins and their modes of regulation may be key for understanding the molecular basis of information storage by synapses.

One synaptic protein with the properties expected of a slot protein is PSD-95 (Schnell et al., 2002). PSD-95 is attached to the postsynaptic membrane directly by palmitoylation (El-Husseini Ael et al., 2002) and indirectly by PDZ interactions with the cytoplasmic tails of NMDARs (reviewed in Sheng, 2001). PSD-95 also binds to stargazin, a protein that escorts AMPARs to the synapse (Chen et al., 2000; Schnell et al., 2002). Via this interaction with stargazin, PSD-95 could potentially act as a docking site for AMPARs at the synapse. Consistent with this notion, overexpression of PSD-95 increases the number of AMPARs at synapses (Schnell et al., 2002). Conversely, removal of PSD-95 from the synapse by depalmitoylation depletes synaptic AMPARs (El-Husseini Ael et al., 2002).

Recent data suggest that NMDAR activation of hippocampal neurons leads to ubiquitination and degradation of PSD-95 by the proteasome (Colledge et al., 2003). This response, like LTD and AMPAR removal, requires Ca^{2+}-dependent dephosphorylation of PKA substrates. Moreover, inhibiting the proteasome, which blocks PSD-95 degradation, prevents NMDA- (Colledge et al., 2003) and AMPA- (Patrick et al., 2003) induced internalization of AMPARs in cultured neurons and reduces synaptically induced LTD in hippocampal slices (Colledge et al., 2003). These and related data suggest that the ubiquitin/proteasome pathway is a critical regulator of the molecular architecture of glutamatergic synapses and therefore the long-term maintenance of LTD and LTP (Burbea et al., 2002; Cline, 2003; Ehlers, 2003; Hegde and DiAntonio, 2002).

In addition to regulated protein degradation, however, there is also evidence that LTD, like LTP, requires protein synthesis for stable expression (Kauderer and Kandel, 2000; Manahan-Vaughan et al., 2000; Sajikumar and Frey, 2003). However, in distinction to late-phase LTP, only inhibitors of mRNA translation, but not transcription, impair stable expression of LTD. A requirement for translation of preexisting mRNA is particularly clear for even the early expression ($<$1 hr) of mGluR-dependent LTD, to be discussed below. It is unknown, however, whether the protein synthesis requirements for NMDAR- and mGluR-dependent LTD are the same, and how the regulated synthesis and degradation of proteins work together to stabilize either type of LTD.

Before leaving the topic of NMDAR-dependent LTD, two additional points should be made. First, there is much evidence that NMDAR-mediated transmission is also depressed during LTD (Gean and Lin, 1993; Montgomery and Madison, 2002; Selig et al., 1995; Xiao et al., 1994, 1995), and like depression of the AMPAR-mediated response, this also appears to be expressed by a postsynaptic mechanism (Heynen et al., 2000; Montgomery and Madison, 2002; Philpot and Bear, 2002; Selig et al., 1995). Future molecular models of LTD will need to take these findings into account. The second point is that (unfortunately) the simple demonstration that a form of LTD outside CA1 is blocked by NMDAR antagonists is not sufficient grounds to conclude that it shares the detailed mechanisms we have discussed here. In neocortex, although there is good evidence for a postsynaptically expressed NMDAR-dependent LTD similar to that in CA1 (Dodt et al., 1999), recent findings point to a second, independent mechanism that involves retrograde signaling by endogenous cannabinoids coincident with activation of *presynaptic* NMDARs (Sjostrom et al., 2003). Such endocannabinoid-mediated LTD will be discussed further below.

mGluR-Dependent LTD

It was initially surprising to find that, under the appropriate experimental conditions, LFS of Schaffer collateral-CA1 synapses can trigger, in addition to NMDAR-dependent LTD, mechanistically distinct forms of mGluR-dependent LTD (Bolshakov and Siegelbaum, 1994; Oliet et al., 1997). Of course, the first and best characterized form of mGluR-dependent LTD is that which occurs in the cerebellar cortex at parallel fiber to Purkinje cell synapses when they are stimulated in conjunction with the climbing fiber input (Ito, 1989; Ito et al., 1982). Climbing fiber synapses are very powerful, and their activation leads to a large rise in intracellular Ca^{2+} that is permissive for LTD. However, a key signal that distinguishes active from inactive parallel fiber synapses, and which is required to trigger LTD, is activation of postsynaptic group 1 (Gp1) mGluRs (Linden et al., 1991). Gp1 mGluRs, by definition, stimulate phosphoinositide hydrolysis and are comprised of mGluR1 and mGluR5, which have different tissue and subcellular localization. Induction of cerebellar LTD requires activation of mGluR1 (Aiba et al., 1994; Shigemoto et al., 1994).

The mechanism of an analogous form of LTD, induced in cultured Purkinje neurons by conjunctive depolarization and glutamate application, has been studied in detail, and it has several features in common with the NMDAR-dependent LTD discussed above. The data suggest that conditioning stimulation leads to clathrin-dependent endocytosis of AMPARs comprised of GluR2 and GluR3 (Wang and Linden, 2000) and that this response requires GluR2 phosphorylation at ser-880 (Chung et al., 2003). Serine 880 is phosphorylated by PKC, which is activated in response to mGluR1 activation.

Similarly, in cultured hippocampal neurons, activation of Gp1 mGluRs with the selective agonist DHPG [(RS)-3,5-dihydroxyphenylglycine] can also trigger the rapid

removal of postsynaptic AMPARs (Snyder et al., 2001; Xiao et al., 2001). Moreover, the identical DHPG treatment of hippocampal slices can induce LTD in CA1 that is sensitive to postsynaptic disruption of clathrin-mediated endocytosis (Xiao et al., 2001). Appropriate synaptic stimulation (paired pulses at 1 Hz; PP-LFS) of the Schaffer collaterals can induce mGluR5-dependent (and NMDAR-independent) LTD that occludes the effect of DHPG (Huber et al., 2001). Interestingly, inhibitors of mRNA translation prevent (1) the induction of stable paired-pulse- and DHPG-induced LTD in hippocampal slices (Hou and Klann, 2004; Huber et al., 2000), (2) DHPG-induced loss of postsynaptic AMPARs in cultured hippocampal neurons (Snyder et al., 2001), and (3) parallel fiber-Purkinje cell LTD in cerebellar slices (Karachot et al., 2001). Recent findings also show that several protein synthesis-dependent responses to Gp 1 mGluR activation, including LTD in hippocampal and cerebellar slices, are prevented by inhibitors of extracellular signal-regulated protein kinase (ERK), a subclass of the mitogen-activated protein kinases (MAPKs) (Endo and Launey, 2003; Gallagher et al., 2004; Thiels et al., 2002; Zhao et al., 2004). These findings, taken together, suggest a number of similarities between mGluR-dependent LTD in cerebellum and hippocampus, including a role for protein synthesis and a postsynaptic site of expression. Further evidence that synaptic activation of Gp1 mGluRs can induce a postsynaptic change has come from studies of depotentiation in the hippocampus (Montgomery and Madison, 2002; Zho et al., 2002).

We hasten to add, however, that there also appear to be significant differences among the types of LTD for which AMPAR internalization has emerged as a mechanism. Assuming that the same molecular mechanisms elucidated in cultured Purkinje cells apply to parallel fiber-Purkinje cell synapses in situ, the endocytosis of AMPARs during cerebellar LTD appears to absolutely require GluR2 (Chung et al., 2003), whereas the endocytosis of AMPARs in CA1 pyramidal cells, at least during NMDAR-dependent LTD, still appears to occur in the absence of GluR2 and GluR3 (Jia et al., 1996; Meng et al., 2003). Moreover, although hippocampal mGluR-LTD has not yet been studied in the GluR2/3 knockout mice, DHPG treatment of hippocampal slices generates a form of LTD that is insensitive to PKC inhibitors (Gallagher et al., 2004; Wu et al., 2004). Further evidence for a heterogeneity of cell type-specific mechanisms controlling AMPAR trafficking comes from studies of LTD at excitatory synapses on midbrain dopamine neurons. At these synapses, LTD again involves endocytosis of AMPARs, but in this case, this process appears to be triggered by Ca^{2+}-dependent activation of PKA (Gutlerner et al., 2002).

There is also evidence indicating that there is a second, presynaptically expressed form of mGluR-dependent LTD in the hippocampus that can be induced both by DHPG (Palmer et al., 1997) and by synaptic stimulation (Bolshakov and Siegelbaum, 1994). In brief, it has been shown in slices from young rats that activation of mGluR5 with DHPG (Doherty et al., 2000; Faas et al., 2002) causes a lasting increase in the paired-pulse ratio and the coefficient of variation of EPSCs and a decrease in the success rate of dendritically recorded EPSCs without affecting their potency (Fitzjohn et al., 2001). Although presynaptic Ca^{2+} transients are not persistently altered (Faas et al., 2002; but see Watabe et al., 2002), presynaptic vesicle release is reduced (Zakharenko et al., 2002). Moreover, under these conditions, the postsynaptic sensitivity to AMPA and glutamate are not altered (Rammes et al., 2003; Tan et al., 2003). Together, these findings make a strong case for a presynaptic expression mechanism for this second form of mGluR-dependent LTD. Since mGluR5 is largely postsynaptic in CA1 and selective postsynaptic manipulations disrupt presynaptically expressed LTD (Watabe et al., 2002), a retrograde messenger must be involved. The leading candidates are 12-lipoxygenase metabolites of arachidonic acid (Feinmark et al., 2003).

In some respects, the situation for mGluR-dependent LTD today resembles the confusion that existed 10 years ago, before reliable protocols were developed to isolate and study mGluR- and NMDAR-dependent LTD independently (Huber et al., 2000; Kemp and Bashir, 1997; Oliet et al., 1997). Investigation of what are apparently multiple forms of mGluR-dependent LTD in CA1 would be aided by a systematic effort to get to the bottom of what experimental variables tip the balance from one type to another. Hints from the existing literature are differences in developmental expression (the presynaptic form is the more immature) and differential dependence on p38 MAP kinase (presynaptic LTD; Bolshakov et al., 2000; but see Zhu et al., 2002) and ERK (postsynaptic LTD; Gallagher et al., 2004).

Endocannabinoid-Mediated LTD

The discovery of G protein-coupled receptors that bind Δ^9-tetrahydrocannabionol, the psychoactive ingredient of the marijuana plant *Cannabis sativa*, suggested the existence in the brain of some endogenous signaling molecules that could activate these receptors. It is now clear that endogenous cannabinoid signaling is widespread in the brain and plays important functional roles (Freund et al., 2003). In the hippocampus and cerebellum, release of endocannabinoids from postsynaptic cells causes a short-lasting, presynaptically mediated inhibition of inhibitory synaptic transmission termed "depolarization-induced suppression of inhibition" (DSI) (Kreitzer and Regehr, 2002; Wilson and Nicoll, 2002). In the cerebellum, postsynaptic release of endocannabinoids also transiently depresses excitatory synaptic responses in Purkinje cells via activation of presynaptic cannabinoid (CB) receptors, a phenomenon termed "depolarization-induced suppression of excitation" (DSE) (Kreitzer and Regehr, 2001).

Given that excitatory and inhibitory synapses in the hippocampus and cerebellum are often considered prototypic of synapses throughout the brain, it was surprising to learn that excitatory synapses on medium spiny neurons in the dorsal and ventral striatum as well as between layer V cells in visual cortex express a form of LTD that, like DSI and DSE, depends on postsynaptic release of endocannabinoids, which then act retrogradely on presynaptic CB1 receptors (Gerdeman et al., 2002; Robbe et al., 2002; Sjostrom et al., 2003). In the striatum, this endocannabinoid-mediated LTD (eCB-LTD) requires activation of postsynaptic group I mGluRs (Robbe et al., 2002; Sung et al., 2001). In cortex, eCB-

LTD appears to require not only activation of presynaptic CB1 receptors but also coincident activation of presynaptic NMDARs (Sjostrom et al., 2003).

It remains unclear what is different about the excitatory synapses in striatum and cortex which are capable of expressing eCB-LTD. One possibility is that the duration of the postsynaptic release of endocannabinoids differs for DSI/DSE and eCB-LTD. Consistent with this hypothesis are results from the study of a novel form of LTD that occurs at inhibitory synapses on hippocampal CA1 pyramidal cells, the same synapses that express DSI (Chevaleyre and Castillo, 2003). This I-LTD requires postsynaptic release of endocannabinoids lasting several minutes, suggesting, perhaps, that prolonged activation of presynaptic CB1 receptors at any synapse expressing CB1 receptors is capable of eliciting eCB-LTD. That is, what makes eCB-LTD possible at some synapses but not others is differences in the machinery responsible for the postsynaptic release of endocannabionoids. Additionally, there may be differences at synapses expressing eCB-LTD in how the presynaptic release machinery is modulated by CB1 receptor activation. Given the apparent widespread distribution of eCB-LTD, further intensive investigation of its detailed molecular mechanisms and possible functions seems warranted.

Functions of LTP and LTD: Two Examples

As mentioned in our introduction and indicated by the discussion of LTP and LTD in other reviews in this issue, LTP and LTD remain prime candidates for mediating learning and memory as well as many other forms of experience-dependent plasticity. However, it remains a challenging task to demonstrate that an in vivo experience generates LTP or LTD at some specific set of synapses and that this synaptic modification plays an important functional role. In the last section of this review, we will provide two examples for which there is evidence that LTP or LTD do occur in response to in vivo experiences and play functionally important roles.

Experience-Dependent Plasticity in Developing Sensory Cortex

It is interesting to recall that before the establishment of reliable protocols for LTD induction it was debated whether homosynaptic LTD mechanisms (outside the cerebellum) were even necessary. With sufficiently sparse synaptic potentiation and a mechanism for periodic renormalization of synaptic weights, it seemed plausible that LTD simply did not exist (and, of course, that was why it was difficult to find!). Even in situations where synaptic depression undeniably occurred in vivo, such as in juvenile visual cortex after a period of monocular deprivation, the effect could be plausibly explained by a heterosynaptic renormalization of synaptic weights as a consequence of LTP-like, "Hebbian" modifications of the competing input (Stent, 1973). However, there were theories of cortical plasticity that suggested otherwise. For example, the theory published by Bienenstock, Cooper, and Munro (now called the BCM theory) in 1982 suggested that the depression of deprived-eye inputs in visual cortex was specifically triggered by presynaptic activity when it failed to consistently correlate with a strong evoked postsynaptic response (Bienenstock et al., 1982). Indeed, the BCM theory was the motivation behind the ultimately successful search for homosynaptic LTD in hippocampus and visual cortex (Bear, 2003).

The idea that depression of responses in visual cortex is actually caused by activity in the deprived eye has been tested experimentally. Rittenhouse et al. found that the response depression caused by brief monocular deprivation in kittens was abrogated when tetrodotoxin was injected into the deprived eye (Rittenhouse et al., 1999), and this has recently been confirmed in the mouse. Thus, activity in the deprived afferents must be the trigger for response depression, as assumed in the BCM theory. But how?

Of course, as just reviewed, we now have a multitude of potential mechanisms whereby presynaptic activity can depress synaptic responses. In visual cortex, the search can be narrowed somewhat by the finding that the effects of brief monocular deprivation depend on activation of cortical NMDARs (Bear et al., 1990; Roberts et al., 1998). And, to date, two NMDAR-dependent forms of LTD have been reasonably well characterized in visual cortex. The first seems to bear a close resemblance to the LTD described above in area CA1. It is readily elicited by prolonged low-frequency stimulation (Heynen et al., 2003; Kirkwood et al., 1993), depends on protein phosphatase activation (Kirkwood and Bear, 1994), is associated with dephosphorylation of ser-845 of GluR1 (Heynen et al., 2003), and has a postsynaptic site of expression (Dodt et al., 1999). The second is readily (but not exclusively) elicited by precise pairing of pre- and postsynaptic spikes and requires a rise in postsynaptic $[Ca^{2+}]$ but also depends on coincident activation of presynaptic NMDA and CB1 receptors and has a presynaptic site of expression (Sjostrom et al., 2003, 2004).

The relative contributions of these and other mechanisms to the naturally occurring ocular dominance shift that occurs after monocular deprivation remain to be parsed out. However, a recent study has provided evidence that the familiar form of NMDAR-dependent LTD observed in CA1 does in fact occur in rat visual cortex after a brief period of monocular deprivation. Heynen et al. (2003) found that brief monocular deprivation causes changes in AMPAR phosphorylation and surface expression in visual cortex that precisely mimic those that occur after LTD. Moreover, like deprivation-induced depression, these changes were observed only during a postnatal critical period, depended on activation of NMDARs, and failed to occur if tetrodotoxin was injected into the deprived eye.

Additional evidence that the mechanisms of LTD are engaged by sensory deprivation has come from studies in slices ex vivo. The logic is that, if deprivation utilizes and partially exhausts the mechanisms of LTD in vivo, there should be less LTD observed at saturation in vitro. Two studies have recently provided this type of evidence, one in visual cortex (Heynen et al., 2003) and the other in somatosensory "barrel" cortex (Allen et al., 2003). Finally, an elegant analysis of the cortical activity patterns caused by deprivation in the somatosensory system revealed the emergence of altered pre- and postsynaptic spiking in vivo (Celikel et al., 2004) that has been shown to cause LTD in vitro (Feldman, 2000). These findings suggest that the eCB-LTD mechanisms may also be engaged by sensory deprivation.

Naturally occurring response potentiation can also be observed in sensory cortex. For example, chronic recordings from adult mouse visual cortex have shown that closing one eye enables a gradual experience-dependent enhancement of the responses to stimulation of the other eye. The effect persists for many days after opening the deprived eye and fails to occur in mice with reduced expression of NMDARs in the superficial layers of visual cortex (Sawtell et al., 1999). Clearly, this change is a form of "LTP," but whether it utilizes the familiar mechanisms of NMDAR-dependent LTP in CA1 remains to be determined. However, recent studies in rat barrel cortex suggest that it might. Takahashi et al. (2003) showed that sensory experience drives recombinant GluR1 into synapses between layer 4 and layer 3 neurons. Moreover, expression of the GluR1 cytoplasmic tail, a construct that prevents synaptic delivery of AMPARs during LTP in CA1, blocked experience-driven synaptic potentiation (Takahashi et al., 2003).

Synaptic Plasticity and Addiction

The defining characteristic of drug addiction is persistent and compulsive seeking and ingestion of drugs despite severe adverse consequences. While phenomena such as tolerance, dependence, and withdrawal certainly have important clinical consequences, the major problem in addiction treatment is the long-lasting risk of relapse which commonly is triggered by exposure to drug-related cues. Thus, it has become apparent that the neural mechanisms underlying adaptive forms of learning and memory likely also play a critical role in the pathophysiology of addiction (Berke and Hyman, 2000; Hyman and Malenka, 2001; Nestler, 2001). Another article in this issue of *Neuron* (Kelley, 2004) addresses in detail the role of memory mechanisms in addiction. We will therefore limit our discussion to the evidence that LTP and LTD at specific synapses play roles in mediating some of the behavioral consequences of in vivo administration of drug of abuse.

It is well established that a key site of action of drugs of abuse is the mesolimbic dopamine (DA) system consisting of the ventral tegmental area (VTA) and nucleus accumbens (NAc) and that excitatory synaptic transmission in these structures is critical for mediating several different forms of long-lasting, drug-induced behavioral plasticity (Berke and Hyman, 2000; Everitt and Wolf, 2002; Hyman and Malenka, 2001; Kelley and Berridge, 2002; Nestler, 2001; Vanderschuren and Kalivas, 2000). Thus, it seems reasonable to hypothesize that plasticity at these excitatory synapses plays an important role in mediating some of the behavioral consequences of exposure to drugs of abuse. Indeed, it is now established that various forms of LTP and LTD can be elicited at excitatory synapses in the VTA and NAc (for reviews, see Gerdeman et al., 2003; Kauer, 2004; Thomas and Malenka, 2003). The important question, however, is whether in vivo exposure to drugs of abuse actually elicit LTP or LTD-like synaptic modifications in the mesolimbic DA system.

This issue is beginning to be addressed by treating animals with drugs of abuse and then preparing in vitro slices of the VTA or NAc that permit direct assays of changes in synaptic strength. Surprisingly, it was found that administration of a single dose of several different classes of drugs of abuse cause a significant increase in synaptic strength at excitatory synapses on DA cells in the VTA (Faleiro et al., 2004; Saal et al., 2003; Ungless et al., 2001). This increase appears to share mechanisms with LTP in the VTA and, like NMDAR-dependent LTP in the hippocampus, involves the upregulation of AMPARs (Ungless et al., 2001). It lasts somewhere between 5 and 10 days (Ungless et al., 2001), but repeated administration of cocaine does not increase the magnitude nor the duration of the drug-induced synaptic potentiation (Borgland et al., 2004).

Several lines of evidence suggest that this drug-induced "LTP" at excitatory synapses on DA cells in the VTA plays a functional role in triggering or mediating some drug-induced behavioral adaptations. First, injection of glutamate receptor antagonists into the VTA blocks the development of behavioral sensitization (Carlezon and Nestler, 2002; Everitt and Wolf, 2002; Vanderschuren and Kalivas, 2000) as well as conditioned place preference (Harris and Aston-Jones, 2003), two prominent animal models for core features of addiction. Second, a knockout mouse lacking the AMPAR subunit GluR1 does not express the cocaine-induced potentiation of synaptic strength in the VTA and also lacks conditioned place preference to cocaine (Dong et al., 2004). This is consistent with work showing that overexpression of GluR1 in the VTA enhances the rewarding or motivational effects of morphine and cocaine (Carlezon et al., 1997; Choi et al., 2003). Conversely, overexpression of a mutant form of GluR1 that had been shown to not be delivered to synapses (Esteban et al., 2003) reduced the reinforcing efficacy of cocaine (Choi et al., 2003). These results suggest that the drug-induced LTP in VTA DA cells may play an important, albeit transient, role in enhancing the reinforcing or motivational properties of drugs of abuse as addiction develops. A caveat to this conclusion, however, is that knockout mice lacking GluR1 still exhibit robust behavioral sensitization in response to repeated exposure to psychostimulants (Dong et al., 2004; Vekovischeva et al., 2001), indicating either that developmental compensations in the VTA have occurred or that GluR1-dependent processes do not play a role in this specific form of drug-induced behavioral plasticity.

Although less work has been done on the long-term effects of in vivo exposure to drugs of abuse on excitatory synaptic transmission in the NAc, there also is evidence that drug-induced synaptic plasticity occurs in this structure. Specifically, chronic in vivo cocaine administration was found to cause a postsynaptically mediated decrease in synaptic strength in medium spiny neurons in the NAc shell, a decrease that appears to share mechanisms with one of the forms of LTD observed in this structure (Thomas et al., 2001). The functional role of this drug-induced LTD needs to be explored more thoroughly, but several behavioral findings suggest that it may indeed be important. First, injection of glutamate receptor antagonists into the NAc disrupts the expression of behavioral sensitization as well as other drug-evoked behaviors (Everitt and Wolf, 2002; Kelley and Berridge, 2002; Vanderschuren and Kalivas, 2000). Second, overexpression of GluR1 in the NAc facilitates extinction of cocaine-seeking responses (Sutton et al., 2003) and makes cocaine aversive, rather than rewarding, in a conditioned place preference assay (Kelz

et al., 1999). This molecular manipulation would be expected to increase synaptic strength and thus oppose the LTD elicited by chronic cocaine exposure.

In addition to eliciting plasticity at excitatory synapses in the VTA and NAc, drugs of abuse can also modify the triggering of LTP and LTD. For example, single or repetitive in vivo administration of THC suppresses eCB-LTD in the NAc (Hoffman et al., 2003; Mato et al., 2004), perhaps due to functional tolerance of CB1 receptors (Mato et al., 2004). Amphetamine, on the other hand, blocks LTD in the VTA (Jones et al., 2000), an action that would be expected to facilitate the generation of LTP. Nicotine, via presynaptic effects on glutamate release, also can enhance the generation of LTP in the VTA (Mansvelder and McGehee, 2000).

Clearly, it is early days in our understanding of the functional roles of drug-induced synaptic plasticity in the mesolimbic DA system. Nonetheless, there are several attractive features to using the behavioral plasticity elicited by in vivo exposure to drugs of abuse as a model for probing the potential functional roles of LTP and LTD. The behavioral effects elicited by drugs of abuse are robust and often very long lasting. Furthermore, many of the assays used to study the behavioral effects of drugs of abuse are relatively straightforward. Many of the key sites in the brain that mediate the long-lasting behavioral effects of drugs of abuse are also well established, as are the molecular targets of these drugs. Finally, understanding the synaptic adaptations elicited by drugs of abuse will not only provide mechanistic information about how neural circuit modifications mediate experience-dependent plasticity but also will accelerate our understanding of the pathophysiology of a common and devastating neuropsychiatric disorder.

Concluding Remarks

The preceding examples underscore the utility and promise of studying LTD and LTP. By elucidating their underlying mechanisms, it now seems possible to reconstruct, at least in broad outline, some of the subcellular events that are triggered by experience and deprivation to alter cortical function, and by drug exposure to alter behavior. The coming decade will undoubtedly bring further clarification of diverse LTP and LTD mechanisms and how they contribute to adaptive brain function. An exciting prospect is that knowledge of the molecular mechanisms for LTP and LTD, combined with a more sophisticated understanding of the neural circuits in which they operate, will yield new insights into the molecular pathology of diseases of the synapse, ranging from mental retardation to drug addiction to Alzheimer's disease.

Acknowledgments

Work in the authors' labs is supported by NIMH (R.C.M. and M.F.B.), NIDA (R.C.M.), NEI (M.F.B.), and the Howard Hughes Medical Institute (M.F.B.). We thank P. Castillo, A. Kreitzer, R. Nicoll, and T. Sudhof for helpful comments. We apologize to those colleagues whose work we failed to cite because of the large scope of this review and significant space limitations.

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