Neuropsychopharmacology REVIEWS (2008) 33, 18–41
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Synaptic Plasticity: Multiple Forms, Functions, and Mechanisms

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Experiences, whether they be learning in a classroom, a stressful event, or ingestion of a psychoactive substance, impact the brain by modifying the activity and organization of specific neural circuitry. A major mechanism by which the neural activity generated by an experience modifies brain function is via modifications of synaptic transmission; that is, synaptic plasticity. Here, we review current understanding of the mechanisms of the major forms of synaptic plasticity at excitatory synapses in the mammalian brain. We also provide examples of the possible developmental and behavioral functions of synaptic plasticity and how maladaptive synaptic plasticity may contribute to neuropsychiatric disorders.
Neuropsychopharmacology Reviews (2008) **33,** 18–41; doi:10.1038/sj.npp.1301559; published online 29 August 2007

Keywords: long-term potentiation; long-term depression; NMDA receptors; AMPA receptors; hippocampus; addiction

INTRODUCTION

One of the most important and fascinating properties of the mammalian brain is its plasticity; the capacity of the neural activity generated by an experience to modify neural circuit function and thereby modify subsequent thoughts, feelings, and behavior. Synaptic plasticity specifically refers to the activity-dependent modification of the strength or efficacy of synaptic transmission at preexisting synapses, and for over a century has been proposed to play a central role in the capacity of the brain to incorporate transient experiences into persistent memory traces. Synaptic plasticity is also thought to play key roles in the early development of neural circuitry and evidence is accumulating that impairments in synaptic plasticity mechanisms contribute to several prominent neuropsychiatric disorders. Thus, elucidating the detailed molecular mechanisms underlying synaptic plasticity in any number of different brain regions is critical for understanding the neural basis of many aspects of normal and pathological brain function.

Given the diversity of the functions ascribed to synaptic plasticity, it is not surprising that many forms and mechanisms of synaptic plasticity have been described. Synaptic transmission can be either enhanced or depressed by activity, and these changes span temporal domains ranging from milliseconds to hours, days, and presumably even longer. Furthermore, virtually all excitatory synapses in the mammalian brain simultaneously express a number of different forms of synaptic plasticity. Here, we attempt to provide a broad overview of the mechanisms of the most prominent forms of plasticity observed at excitatory synapses in the mammalian brain. After briefly reviewing short-lasting forms of synaptic plasticity, we will emphasize current understanding of the cellular mechanisms and possible functions of the class of phenomena commonly termed long-term potentiation (LTP) and long-term depression (LTD).

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Received 5 June 2007; revised 1 August 2007; accepted 1 August 2007

SHORT-TERM SYNAPTIC PLASTICITY

Numerous forms of short-term synaptic plasticity, lasting on the order of milliseconds to several minutes, have been observed at virtually every synapse examined in organisms ranging from simple invertebrates to mammals (Zucker and Regehr, 2002). These are thought to play important roles in short-term adaptations to sensory inputs, transient changes in behavioral states, and short-lasting forms of memory. Most forms of short-term synaptic plasticity are triggered by short bursts of activity causing a transient accumulation of calcium in presynaptic nerve terminals. This increase in presynaptic calcium in turn causes changes in the probability of neurotransmitter release by directly modifying the biochemical processes that underlie the exocytosis of synaptic vesicles.

Paired-Pulse Facilitation and Depression

When two stimuli are delivered within a short interval, the response to the second stimulus can be either enhanced or

depressed relative to the response to the first stimulus (Katz and Miledi, 1968; Zucker and Regehr, 2002). Paired-pulse depression is commonly observed at all synapses at short (less than 20 ms) interstimulus intervals, and most probably results from inactivation of voltage-dependent sodium or calcium channels or from a transient depletion of the release-ready pool of vesicles docked at the presynaptic terminal. Many synapses exhibit paired-pulse facilitation at longer interstimulus intervals (20–500 ms). A simple explanation for this phenomenon is that the residual calcium left over from the invasion of the first action potential contributes to additional release during the second stimulation, but it is likely that additional mechanisms are involved. These may involve activation of protein kinases that modulate the activity of presynaptic phosphoproteins. For example, mice in which the presynaptic phosphoprotein synapsin (De Camilli *et al*, 1990) has been knocked out, exhibit abnormal short-term plasticity (Rosahl *et al*, 1993, 1995).

Whether a synapse exhibits paired-pulse facilitation or depression depends on the recent history of activation of the synapse. Because these forms of plasticity largely result from changes in the probability of transmitter release (p), synapses that begin with a very high p tend to depress their response to the second pulse (Dobrunz and Stevens, 1997). In contrast, synapses with a low initial p normally exhibit an increase in p in response to the second stimulus. Consistent with this idea, manipulations that decrease p (eg, activation of presynaptic autoreceptors) almost always cause an increase in the magnitude of paired-pulse facilitation, or even a conversion of paired-pulse depression to facilitation. Thus, the same synapse can display either facilitation or depression, depending on its recent history of activation and modulation.

Facilitation and Depression Following Trains of Stimuli

Longer-lasting forms of plasticity are observed following repetitive or tetanic stimulation of synapses with prolonged (approximately 200 ms to 5 s) trains of stimulation applied at high frequencies (10–200 Hz) (Zucker and Regehr, 2002). Augmentation and post-tetanic potentiation (PTP) describe an enhancement of transmitter release lasting from seconds (augmentation) to several minutes (PTP). They also involve an increase in the probability of transmitter release in response to an action potential due, in large part, to the buildup of calcium concentration in the presynaptic terminal during the stimulus trains. This residual calcium may combine with the calcium influx elicited by the subsequent single action potential to enhance directly the release of neurotransmitter, or may lead to biochemical modifications of proteins in the presynaptic terminal (Magleby and Zengel, 1982; Zucker and Regehr, 2002).

At some synapses, repetitive activation leads to depression that can last for several seconds or even minutes (Betz, 1970; Zucker and Regehr, 2002). As in paired-pulse depression, this generally occurs in synapses that exhibit a high probability of release, and is thought to result, at least in part, from a transient depletion of the release-ready pool of synaptic vesicles. The decrease in synaptic strength can also arise from the release of modulatory substances from the activated presynaptic terminals, postsynaptic cells, or even neighboring cells, initiating a signaling cascade that leads to inhibition of the presynaptic release machinery. Finally, a postsynaptic mechanism of short-term plasticity may involve desensitization of ligand-gated receptors, making the target neuron less sensitive to neurotransmitter. A key characteristic of depression at many synapses is use dependence. Higher levels of transmission are associated with larger depression, and reduction of baseline transmission (eg, by reducing external calcium concentration) relieves depression.

Modulation of Transmission by Presynaptic Receptors

Most presynaptic terminals possess a number of different types of metabotropic G-protein-coupled receptors, as well as ionotropic receptors (MacDermott *et al*, 1999). The probability of transmitter release, a significant factor in defining synaptic strength, is controlled in part by the occupancy of these receptors, which in turn is set by the extracellular concentrations of their agonists. In some cases, tonic levels of endogenous ligands are sufficient to partially activate the receptors. Nonetheless, synaptic activity can further increase receptor occupancy by transiently elevating the concentration of various presynaptic neuromodulators (Thompson *et al*, 1993; Miller, 1998). Depending on their specific properties, activation of these receptors can either enhance or depress synaptic transmission.

Via the release of a number of different neuromodulators, postsynaptic cells can also influence the release of transmitter from presynaptic terminals. A common scenario is that in response to strong postsynaptic depolarization, dendrites release retrograde messengers that act through G-protein-coupled receptors located on presynaptic terminals to influence neurotransmitter release. Retrograde messengers that have been identified in specific cell types include dopamine, dynorphin, glutamate, GABA, nitric oxide, brain-derived neurotrophic factor (BDNF), and oxytocin (Drake *et al*, 1994; Kombian *et al*, 1997; Llano *et al*, 1991; Naggapan and Lu, 2005; Nugent *et al*, 2007; Pitler and Alger, 1992; Zilberter, 2000; Zilberter *et al*, 1999). Although postsynaptic, calcium-dependent fusion of vesicles is one common mechanism for the release of retrograde messengers, they can also released by non-vesicular mechanisms. For example, a widespread, extensively studied system for mediating retrograde synaptic signaling involves the postsynaptic release of endogenous cannabinoids, such as anandamide and 2-arachidonoylglycerol, which are produced upon demand by cleavage of phospholipids and are sensed by CB1 receptors on presynaptic terminals. The mechanisms of endocannabinoid release are unclear and may involve a transporter, which facilitates diffusion across the plasma membrane (Chevaleyre *et al*, 2006) Such retrograde signaling by postsynaptic release of endocannabinoids can be initiated by strong depolarization or activation of postsynaptic metabotropic receptors and has been shown to transiently suppress inhibitory and excitatory synapses in several brain regions (Chevaleyre *et al*, 2006). Importantly, in the striatum, there is a form of LTD (to be discussed below) that is triggered by the release of endocannabinoids.

Involvement of Glia in Short-Term Plasticity

There is growing realization that glia may be involved in some forms of short-term plasticity (Araque *et al*, 2001; Haydon, 2001). With their intimate association with synapses, astrocytes and perisynaptic Schwann cells are well positioned to regulate synapses. They have an established role in clearance of neurotransmitter and may participate in synaptic plasticity by controlling the speed and extent of such clearance (Bergles *et al*, 1999; Danbolt, 2001). This can in turn impact on the degree of postsynaptic receptor activation and desensitization. Another way that glia may be involved in synaptic plasticity is by sensing extracellular messengers and then releasing substances that in turn can directly affect synaptic efficacy (Araque *et al*, 2001; Haydon, 2001). For example, glia express many different neurotransmitter receptors (eg, glutamate receptors), which when activated result in the release of substances (eg, ATP) that can then act on presynaptic terminals to regulate neurotransmitter release.

Functions of Short-Term Synaptic Plasticity

Short-term synaptic plasticity was originally established as behaviorally important from studies of simple organisms such as Aplysia (Kandel and Tauc, 1965). In the mammalian brain, an important consequence of short-term synaptic plasticity is to influence the information processing function of synapses, enabling them to act as filters with a wide range of properties. For example, synapses with a low initial probability of release function as high-pass filters, since they will facilitate during high-frequency action potential bursts while low-frequency bursts will not be transmitted with the same efficacy. In contrast, synapses with a high initial probability of release function as low-pass filters, since they will depress during high-frequency bursts but will reliably relay low-frequency activity (Abbott and Regehr, 2004). The filtering characteristics of a synapse can be adjusted through modulation of the initial release probability. This most commonly occurs due to the release of neuromodulators that, via activation of presynaptic receptors, reduce the probability of release. This changes the filtering characteristics of the synapse, causing facilitation to become predominant over depression. In this way, presynaptic inhibition can convert a synapse from a low-pass to a high-pass filter.

LONG-TERM SYNAPTIC PLASTICIY

It is widely believed that experience of any sort modifies subsequent behavior at least in part through activity-dependent, long-lasting modifications of synaptic strength. The brain encodes external and internal events as complex, spatio-temporal patterns of activity in large ensembles of neurons that can be conceptualized as 'neural circuits'. A key feature defining the behavior of any given neural circuit is the pattern of synaptic weights that connect the individual neurons that comprise the circuit. A corollary to this hypothesis is that new information is stored (ie, memories are generated) when activity in a circuit causes a long-lasting change in the pattern of synaptic weights. This idea was put forward over 100 years ago by the Spanish Nobel laureate Santiago Ramon y Cajal, and was further advanced in the late 1940s by Donald Hebb, who proposed 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). This proposed function for synaptic plasticity, forming a memory trace following the detection of two coincident events, suggests an appealing cellular basis for behavioral phenomena such as Pavlovian classical conditioning (Pavlov, 1927).

Experimental support for the very existence of such long-lasting, activity-dependent changes in synaptic strength was lacking until the early 1970s when Bliss and colleagues (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973) reported that repetitive activation of excitatory synapses in the hippocampus caused a potentiation of synaptic strength that could last for hours or even days. Over the last three decades, this phenomenon, eventually termed LTP, has been the object of intense investigation because it is widely believed that it provides an important key to understanding some of the cellular and molecular mechanisms by which memories are formed (Martin *et al*, 2000; Pastalkova *et al*, 2006; Whitlock *et al*, 2006).

Although still considered prototypic, it is now clear that hippocampal LTP is only one of several different forms of long-term synaptic plasticity that exist in specific circuits in the mammalian brain. Importantly, it is well established that most synapses that exhibit LTP also express one or more forms of LTD. Thus, a key concept is that synaptic strength at excitatory synapses is bidirectionally modifiable by different patterns of activity. Furthermore, it is now clear that the terms 'LTP' and 'LTD' describe a class of phenomena, the underlying mechanisms of which vary depending on the circuits in which they function.

Additional forms of synaptic plasticity more recently identified include homeostatic plasticity (Turrigiano and Nelson, 2004) and metaplasticity (Abraham and Bear, 1996). The major form of homeostatic plasticity is 'synaptic scaling', which describes phenomena whereby the strength of all synapses on a given cell are adjusted in response to prolonged changes in activity. Specifically, prolonged decreases in overall activity cause a net scaling up of total synaptic strengths while prolonged increases in activity cause the opposite, a scaling down of synaptic strengths. This form of plasticity operates on a much slower timescale than LTP or LTD and may be particularly important during the development of neural circuits. Metaplasticity refers to the effects that activity can have on the capacity of synapses to express long-term plasticity.

The most extensively studied and therefore prototypic forms of synaptic plasticity are the LTP and LTD observed in the CA1 region of the hippocampus (Figure 1), which are triggered by activation of *N*-methyl-D-aspartate (NMDA) receptors (NMDARs). We will therefore begin with a discussion of their underlying mechanisms. We will then proceed to reviewing some of the other prominent forms of LTP and LTD for which mechanisms have been most firmly established.

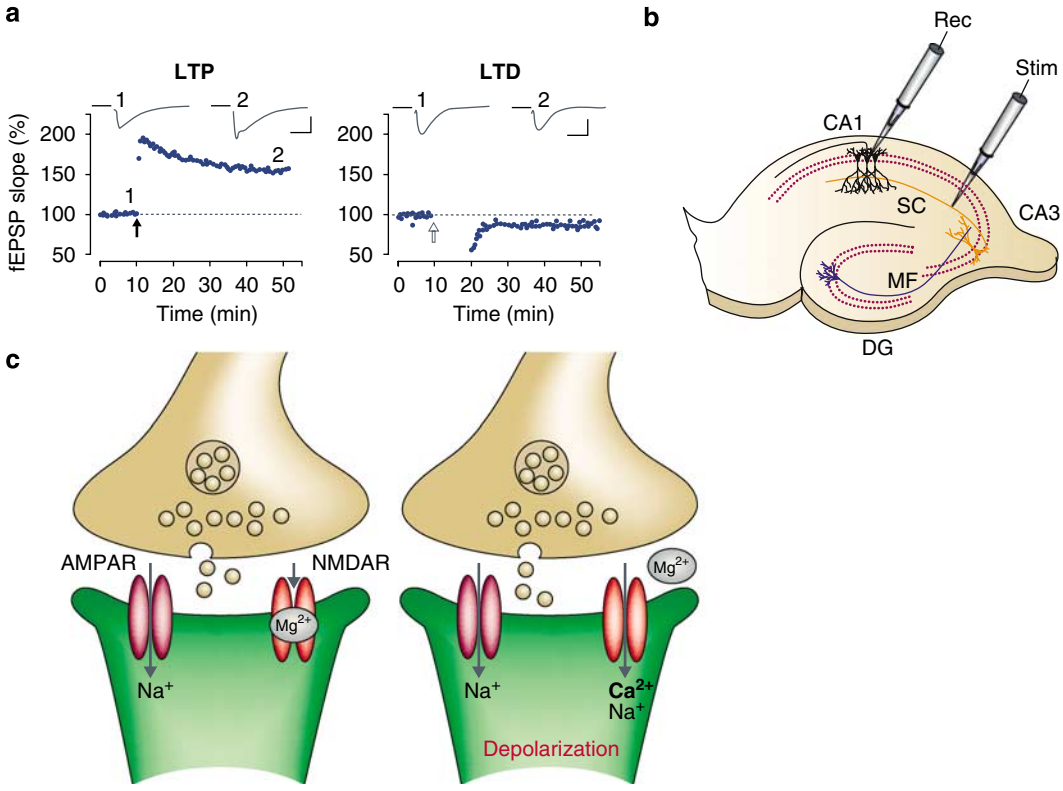

Figure 1 NMDAR-dependent LTP and LTD at hippocampal CA1 synapses. (a) Sample experiments illustrating LTP and LTD in the CA1 region of the hippocampus. Synaptic strength, defined as the initial slope of the field excitatory postsynaptic potential (fEPSP; normalized to baseline) is plotted as a function of time. Left panel demonstrates LTP elicited by high-frequency tetanic stimulation (100 Hz stimulation for 1 s; black arrowhead). Right panel illustrates LTD elicited by low-frequency stimulation (5 Hz stimulation for 3 min given twice with a 3 min interval; open arrow). Data traces were taken at the times indicated by the numbers on the graphs (scale bar: 0.5 mV; 10 ms) (courtesy of W Morishita). (b) A schematic diagram of the rodent hippocampal slice preparation, demonstrating the CA1 and CA3 regions as well as the dentate gyrus (DG). (SC = Schaffer collateral; MF = mossy fiber). Typical electrode placements for studying synaptic plasticity at Schaffer collateral synapses onto CA1 neurons are indicated (Stim = stimulating electrode; Rec = recording electrode). (c) Model of synaptic transmission at excitatory synapses. During basal synaptic transmission (left panel), synaptically released glutamate binds both the NMDA and AMPARs. Na^+ flows through the AMPAR channel but not through the NMDAR channel because of the Mg^{2+} block of this channel. Depolarization of the postsynaptic cell (right) relieves the Mg^{2+} block of the NMDAR channel and allows both Na^+ and Ca^{2+} to flow into the dendritic spine. The resultant increase in Ca^{2+} in the dendritic spine is necessary for triggering the subsequent events that drive synaptic plasticity.

NMDAR-Dependent LTP

No form of plasticity has generated more interest, or been more extensively studied than LTP in the CA1 region of the hippocampus. The excitement surrounding this phenomenon is due to compelling evidence from rodents, primates, and humans associating the hippocampus with a neural system involved in various forms of long-term memory (Martin *et al*, 2000; Zola-Morgan and Squire, 1993). Furthermore, several basic properties of LTP make it an attractive cellular mechanism for rapid information storage. Similar to memory, LTP can be generated rapidly and is strengthened and prolonged by repetition. It also exhibits cooperativity, associativity, and input specificity. (Nicoll *et al*, 1988). Cooperativity means that LTP can be induced by the coincident activation of a critical number of synapses. Associativity is the capacity to potentiate a weak input (a small number of synapses) when it is activated in association with a strong input (a larger number of synapses). As such, associativity is a cellular analogue of classical conditioning and is an implicit property of the so-called Hebbian synapse. Input specificity indicates that LTP is elicited only at activated synapses and not at adjacent, inactive synapses on the same postsynaptic cell. This feature dramatically increases the storage capacity of individual neurons since different synapses on the same cell can be involved in separate circuits encoding different bits of information.

A major technological advance in the study of synaptic plasticity was the development of the hippocampal slice preparation that made LTP accessible to rigorous experimental analysis (Figure 1b). Indeed, the bulk of our knowledge on the molecular mechanisms of LTP has been derived from studies of LTP at excitatory synapses on CA1 pyramidal neurons in hippocampal slices. Similar or identical forms of LTP have been observed at excitatory synapses throughout the brain. Thus, the conclusions drawn from the study of LTP in the hippocampal CA1 region are often applied to other brain regions.

Triggering NMDAR-dependent LTP. A major advance in the understanding of excitatory synaptic function and LTP was the demonstration that two major types of ionotropic glutamate receptors contribute to the postsynaptic response at glutamatergic synapses, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (AMPARs) and NMDARs (Figure 1c). These receptors are often (although not always, as will be elaborated upon later) found

colocalized on individual dendritic spines. The AMPAR has a channel that is permeable to monovalent cations (Na^+ and K^+), and activation of AMPARs provides most of the inward current that generates the excitatory synaptic response when the cell is close to its resting membrane potential. In contrast to AMPARs, the NMDAR exhibits a strong voltage dependence because of the block of its channel at negative membrane potentials by extracellular magnesium (Mayer *et al*, 1984; Nowak *et al*, 1984). As a result, NMDARs contribute little to the postsynaptic response during basal synaptic activity. However, when the cell is depolarized, magnesium dissociates from its binding site within the NMDAR channel, allowing ions to enter the cell. Importantly, unlike AMPAR channels, the NMDAR channel allows calcium as well as sodium to enter the postsynaptic dendritic spine (Figure 1c).

It is firmly established that the triggering (also termed the induction) of LTP in the CA1 region requires activation of NMDARs during strong postsynaptic depolarization leading to a increase in postsynaptic calcium concentration, which likely has to reach some critical threshold value to activate the biochemical processes necessary for LTP (Malenka, 1991; Malenka and Nicoll, 1993). Experimentally, this is normally achieved by applying high-frequency tetanic stimulation to the synapses or by use of a 'pairing-protocol' during which the postsynaptic cell is directly depolarized while low-frequency synaptic activation is sustained. An additional method for induction of LTP (as well as LTD) involves protocols that generate so-called 'spike-time dependent plasticity' (STDP; Dan and Poo, 2006; Markram *et al*, 1997). In studies of STDP, LTP is induced if afferent stimulation generates a synaptic response within a discrete time window prior to the firing of the postsynaptic cell.

Because its contribution to postsynaptic reponses requires both presynaptic release of glutamate and postsynaptic depolarization due to the simultaneous activation of a population of synapses, the NMDAR is often referred to as a 'coincidence detector'. These properties of NMDARs also explain the basic properties of LTP. Cooperativity and associativity occur because of the requirement for multiple synapses to be activated simultaneously to generate adequate postsynaptic depolarization to remove the magnesium block of the NMDAR. Input specificity is due to the compartmentalized increase in calcium, which is limited to the postsynaptic dendritic spine and does not influence adjacent spines (Nicoll *et al*, 1988).

LTP signal transduction mechanisms. An extensive number of signal transduction molecules have been suggested to play a role in translating the calcium signal that is required to trigger LTP into the long-lasting increase in synaptic strength (Malenka and Bear, 2004; Sanes and Lichtman, 1999). However, only for a handful of these has compelling evidence of a mandatory role in LTP been presented. A major limitation of much of the literature on this topic stems from inadequate distinctions between molecules that are key components of the molecular machinery directly responsible for the triggering of LTP ('mediators'), and those molecules which may modulate the ability to generate LTP, or play a permissive role ('modulators'). Some basic criteria that can be suggested for defining the role of a protein as a mediator of LTP induction are: (1) blocking the activation of the molecule during LTP induction blocks LTP; and (2) activation of the molecule induces a potentiation of synaptic transmission, which occludes further synaptic induction of LTP.

Strong evidence indicates that calcium/calmodulin (CaM)-dependent protein kinase II (CaMKII) fulfills these requirements and is a key component of the molecular machinery for LTP. CaMKII undergoes autophosphorylation after the triggering of LTP (Barria *et al*, 1997; Fukunaga *et al*, 1995), and LTP induction was prevented both in knockout mice lacking a critical CaMKII subunit (Silva *et al*, 1992), and in knock-in animals in which endogenous CaMKII was replaced with a form lacking the autophosphorylation site (Giese *et al*, 1998). Furthermore, inhibition of CaMKII activity by directly loading postsynaptic cells with peptides that impair CaMKII function blocks LTP (Malenka *et al*, 1989; Malinow *et al*, 1989), whereas acutely increasing the postsynaptic concentration of active CaMKII increases synaptic strength and occludes LTP (Lledo *et al*, 1995; Pettit *et al*, 1994).

Several other kinases have been implicated in the triggering of LTP, but the experimental evidence supporting their role is not as well substantiated as that for CaMKII. Activation of the cyclic adenosine monophosphate-dependent protein kinase (PKA), perhaps by the activation of a calmodulin-dependent adenylyl cyclase, has been suggested to boost the activity of CaMKII indirectly by decreasing competing protein phosphatase activity (Blitzer *et al*, 1998; Lisman, 1989; Makhinson *et al*, 1999). This presumably happens by phosphorylation of inhibitor 1, an endogenous inhibitor of protein phosphatase 1 (PP1). The extracellular signal-regulated kinase (Erk)/mitogen-activated protein kinase (MAPK) pathway has also been suggested to be important for LTP, as well as some forms of learning and memory (Sweatt, 2004; Thomas and Huganir, 2004). In addition, Src kinase has been implicated in the enhancement of NMDAR function during LTP induction (Kalia *et al*, 2004). Finally, protein kinase C and in particular the atypical PKC isozyme, PKMζ, has received attention because this isozyme is rapidly expressed upon induction of LTP and recent studies have implicated PKMζ in the maintenance of the late phase of LTP both in hippocampal slices and *in vivo* (Hrabetova and Sacktor, 1996; Ling *et al*, 2002; Pastalkova *et al*, 2006; Serrano *et al*, 2005).

Obviously, it remains a very challenging task to be able to definitively identify the key intracellular signaling cascades responsible for the triggering of LTP. Recent technical advances in mass spectrometric techniques for the profiling of post-transcriptional modifications in mixed populations of proteins, as well as the practicality of RNAi approaches for knockdown of candidate proteins, should help further characterize the major LTP players and their dynamic interplay.

Expression mechanisms of LTP. In the past, a major point of contention was whether LTP was primarily expressed postsynaptically as a change in AMPAR properties or presynaptically, as a change in the probability of transmitter release. This latter expression mechanism garnered significant attention because it required the production of a retrograde messenger that was released by postsynaptic

cells and acted on presynaptic terminals (for a thorough review of the evidence for either locus of expression, see Nicoll, 2003). To a large extent, this controversy has been resolved, with the emerging consensus that the major mechanism of expression of LTP at hippocampal CA1 synapses involves an increase in the numbers of AMPARs within the postsynaptic density, driven through activity-dependent changes in AMPAR trafficking (Bredt and Nicoll, 2003; Derkach *et al*, 2007; Malenka and Nicoll, 1999; Malinow and Malenka, 2002; Song and Huganir, 2002). A major contribution to ending the controversy was the proposal of the silent synapse hypothesis and the evidence supporting it (Durand *et al*, 1996; Isaac *et al*, 1995; Liao *et al*, 1995; Malenka and Nicoll, 1997). Silent synapses are synapses that contain only NMDARs with few or no AMPARs, such that at normal resting membrane potentials these synapses exhibit no detectable postsynaptic responses to synaptically released glutamate. The 'unsilencing' of these synapses during the induction of LTP is thought to occur through the incorporation of AMPARs into the postsynaptic plasma membrane. This hypothesis was quickly expanded to include synapses that already contained AMPARs and has led to a large investigative effort into the molecular mechanisms regulating the trafficking of AMPARs (Bredt and Nicoll, 2003; Collingridge *et al*, 2004; Malinow and Malenka, 2002; Sheng and Kim, 2002; Song and Huganir, 2002).

Most AMPARs in the central nervous system are tetramers comprised of four glutamate receptor subunits, GluR1–GluR4. Although these subunits are highly homologous, both the functional properties of AMPARs and their trafficking has been suggested to depend on their subunit composition (Collingridge *et al*, 2004; Derkach *et al*, 2007; Malinow and Malenka, 2002). In the adult hippocampus, two forms of AMPARs are thought to predominate: GluR1/GluR2 heteromers and GluR2/GluR3 heteromers (Wenthold *et al*, 1996). Based on clever overexpression studies, one prominent hypothesis suggests that subunit-specific rules govern the synaptic delivery of AMPARs (Hayashi *et al*, 2000; Passafaro *et al*, 2001; Shi *et al*, 2001). Specifically, it has been suggested that the insertion of GluR1-containing AMPARs into synapses is slow under basal conditions and is strongly stimulated by NMDAR activation, whereas insertion of GluR2/3 heteromeric receptors may occur constitutively on a much more rapid timescale.

Where do these new AMPARs come from and how is their trafficking regulated at a molecular level? Current evidence suggests that recycling endosomes in the dendrites contain a reserve pool of AMPARs that are mobilized during LTP via a process that requires the small GTP-binding protein, Rab11a (Park *et al*, 2004) (Figure 2). Surprisingly, AMPARs do not appear to be inserted directly into the postsynaptic density (PSD) but rather are exocytosed at perisynaptic sites. They then can laterally diffuse in the plasma membrane and be trapped within the PSD due to their interactions with so-called 'slot proteins', which function to trap AMPARs and greatly reduce their lateral mobility. Attractive candidates for these slot proteins are a family of proteins found in the PSD termed MAGUKs (for membrane-associated guanylate kinases). MAGUKS are defined by their multiple protein interaction domains, most importantly so-called PDZ domains. Prominent members of the MAGUK family of PSD proteins include PSD-95, SAP97, PSD-93, and SAP102 (Kim and Sheng, 2004; Montgomery *et al*, 2004). PSD-95 has received the most attention and its level appears to be particularly important for controlling the number of AMPARs at individual synapses as evidenced by the findings that overexpression of PSD-95 increases synaptic strength and occludes LTP (Ehrlich and Malinow, 2004; Stein *et al*, 2003), whereas knockdown of PSD-95 decreases surface expression of AMPARs and synaptic strength (Ehrlich *et al*, 2007; Schluter *et al*, 2006).

The influence of PSD-95, as well as other MAGUKS (Elias *et al*, 2006; Futai *et al*, 2007; Schluter *et al*, 2006), on AMPARs was surprising given that PSD-95 was originally isolated because of its strong interaction with NMDARs (Kornau *et al*, 1995). Another major surprise was that AMPARs do not directly bind to MAGUKs but rather do so via a family of AMPAR auxiliary subunits termed transmembrane AMPAR regulatory proteins (TARPs). TARPs are required for the delivery of AMPARs to the plasma membrane at extrasynaptic sites (Chen *et al*, 2000; Nicoll *et al*, 2006) and also influence their biophysical properties (Tomita *et al*, 2005a). Importantly, they are also required for the synaptic localization of AMPARs due to their direct interaction with MAGUKs (Schnell *et al*, 2002).

The detailed molecular mechanisms by which activation of protein kinases such as CaMKII lead to the synaptic delivery of AMPARs remains to be determined. Phosphorylation of AMPAR subunits themselves by CaMKII does not appear critical (Esteban *et al*, 2003; Lee *et al*, 2003) although other phosphorylation sites, such as the PKA or the PKC sites on GluR1, may be important (Boehm *et al*, 2006; Esteban *et al*, 2003). On the other hand, there is reasonable evidence that phosphorylation of TARPs occurs following CAMKII activation (Tsui and Malenka, 2006) and that this may be critical for LTP (Tomita *et al*, 2005b). It is, however, highly likely that AMPARs and TARPs are just a component of a large complex of proteins, the phosphorylation of which will be required for LTP expression.

LTP also appears to involve a phosphorylation-driven increase in the single-channel conductance of AMPARs themselves (Benke *et al*, 1998; Soderling and Derkach, 2000). Indeed, CaMKII phosphorylates Ser831 in the intracellular C terminus of GluR1, resulting in a significant increase in single-channel conductance of homomeric GluR1 receptors (Derkach *et al*, 1999, 2007). However, one important caveat of this conclusion is that synaptic GluR1-containing AMPARs also contain GluR2, and in GluR1/2 heteromeric AMPARs, the enhanced conductance upon phosphorylation by CaMKII is absent (Oh and Derkach, 2005).

Although the evidence to date suggests a more prominent role for AMPAR exocytosis, the relative contribution of AMPAR trafficking and changes in the biophysical properties of AMPARs to the increase in synaptic strength during LTP are not well defined. One model for the successive events occurring during the first hour of LTP involves activation of calcium-dependent signal transduction pathways, notably CaMKII, resulting in phosphorylation of GluR1-containing receptors and an increase in their single-channel conductance. Roughly simultaneously, AMPARs are translocated into the PSD via exocytosis and lateral

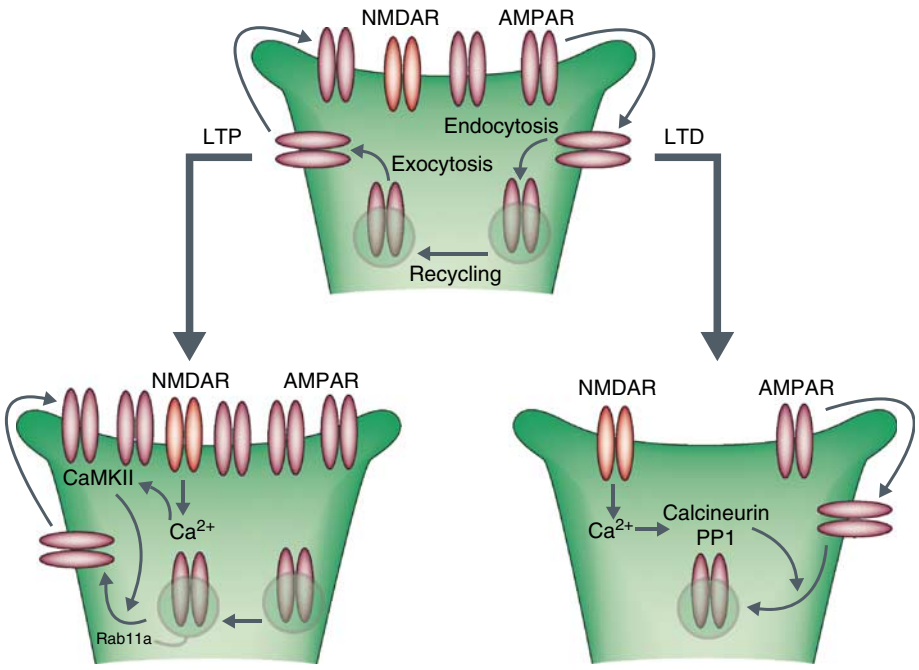

Figure 2 Model of AMPAR trafficking during LTP and LTD. In the basal state (depicted on top), receptors cycle between the postsynaptic membrane and intracellular compartments. This is achieved through lateral mobility of the receptors out of the synapse into endocytic zones, where they are endocytosed into early endosomes in a clathrin- and dynamin-dependent manner. Normally, the receptors are transferred to recycling endosomes and returned to the plasma membrane by exocytosis, followed by lateral movement into the synapse where they are retained through interaction with MAGUKs. Following induction of LTP, there is enhanced receptor exocytosis and stabilization at the synapse through a calcium-driven process that involves CAMKII and fusion of recycling endosomes mediated by Rab11a. Following the induction of LTD, enhanced endocytosis at extrasynaptic sites occurs in a process that is calcium-dependent and involves protein phosphatases, primarily calcineurin and protein phosphatases 1 (PP1). While in the basal state endocytosis is presumably balanced by receptor recycling, following LTD receptors are retained within the cell, and perhaps degraded.

movement within the plasma membrane. Most investigators believe that the incorporation of AMPARs into the PSD is the more important change because it appears to be accompanied by structural changes in the dendritic spines and synapses themselves, an attractive mechanism for maintaining LTP (see below). There are also experimental findings consistent with rapid presynaptic changes during LTP, but the retrograde messenger that is responsible remains elusive, one prominent possibility being BDNF (Bramham and Messaoudi, 2005).

Maintaining LTP. Much of the work on NMDAR-dependent LTP has focused on the mechanisms responsible for its initial 30–60 min, to a large extent because of technical limitations in the duration over which stable electrophysiological recordings can be maintained. Nonetheless, the mechanisms that allow LTP to persist for hours, days, or even longer are of great importance. Like virtually all cell biological phenomena, the persistence of LTP is dependent upon new protein synthesis (Reymann and Frey, 2007). This so-called 'late phase of LTP' (defined as the potentiation present more than 1–2 h after LTP induction) is commonly assumed to depend upon local dendritic protein synthesis, which supplies needed components to the synapse (Sutton and Schuman, 2006), as well as transcription in the nucleus (Zhou *et al*, 2006). The signaling to the nucleus required for long-lasting LTP has been suggested to depend on a number of protein kinases including PKA, CaMKIV, and Erk-MAPK, which activate key transcription factors that may include cAMP response element-binding protein and immediate-early genes such as c-Fos and Zif268/Egr-1 (Thomas and Huganir, 2004). These transcriptional complexes presumably promote expression of effector genes that are required for maintaining the synaptic enhancement.

Several mRNAs can be found in dendrites, including those of the AMPARs themselves, CaMKII, Arc, and proteins which may function to regulate receptor trafficking (Grooms *et al*, 2006; Job and Eberwine, 2001; Ju *et al*, 2004; Mayford *et al*, 1996; Schuman *et al*, 2006; Steward and Schuman, 2001). The trafficking of some of these mRNAs and their local translation seems to be highly regulated by activity. Furthermore, other components of the translational machinery are found in or adjacent to dendritic spines and polyribosomes are recruited to spine heads following LTP induction (Bourne *et al*, 2007). Thus, there is accumulating evidence that the machinery to provide local, newly synthesized proteins to synapses is available.

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 increase in synaptic strength (Frey and Morris, 1997). However, little is known about the identity of the synaptic tag or the newly synthesized proteins that are required to maintain LTP, although it has been suggested that PKA, CAMKII, or PKMζ might function as the synaptic tag (Reymann and Frey, 2007; Sajikumar *et al*, 2005; Young *et al*, 2006).

A compelling possibility for a long-term maintenance mechanism of LTP is the structural remodeling of

potentiated synapses (Luscher *et al*, 2000). Spines come in a variety of shapes and sizes, and can undergo rapid shape changes that are influenced by activity (Yuste and Bonhoeffer, 2001). Morphological changes which have been reported to accompany LTP include growth of new dendritic spines, enlargement of preexisiting spines and their PSDs, and the splitting of single PSDs and spines into two functional synapses (Abraham and Williams, 2003; Matsuzaki *et al*, 2004; Yuste and Bonhoeffer, 2001). An attractive model suggests that during LTP, recycling endosomes contribute AMPAR subunits to the synapse, as well as lipids and constituents which enlarge the synapse (Lisman and Zhabotinsky, 2001; Luscher *et al*, 2000; Park *et al*, 2004, 2006). At some later time point, 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). This presynaptic re-modeling must involve post- and presynaptic protein interactions with likely candidates being cell adhesion molecules such as the cadherins or neuroligin/neurexin interactions.

Summary. The current view of the mechanisms underlying this form of LTP can be summarized as follows (Figure 2). A large NMDAR-dependent increase in dendritic spine calcium concentrations leads to activation of intracellular signaling cascades involving a number of protein kinases, most importantly CaMKII. This leads to an increase in the single-channel conductance of synaptic AMPARs and more importantly, promotes the incorporation of additional AMPARs into the PSD. The new synaptic AMPARs are stabilized through their TARP-mediated interaction with PDZ domain-containing proteins such as PSD-95. In parallel, structural changes within the synapse occur, such that the size of the PSD and dendritic spine are increased. This in turn drives an increase in the size of the presynaptic active zone such that the potentiated synapses are 'permanently' enlarged. The maintenance of these changes for more than a few hours depends on *de novo* transcription as well as local dendritic protein synthesis, presumbably to provide the synapses with a supply of the critical proteins necessary for maintaining synaptic strength.

NMDAR-Dependent LTD

An important advance in the study of long-term synaptic plasticity was the establishment of an experimentally reproducible form of NMDAR-dependent LTD at excitatory synapses on hippocampal CA1 pyramidal cells (Dudek and Bear, 1992). This demonstrated that activity could bi-directionally control synaptic strength (Mulkey and Malenka, 1992), thus providing support for the idea that memories or experiences were encoded by the distribution of synaptic weights in neural circuits, not simply by LTP. Shortly thereafter, a similar form of LTD was observed at neocortical synapses (Kirkwood *et al*, 1993) suggesting that mechanistic studies in the hippocampal CA1 region could provide insights that applied to excitatory synapses throughout the brain. While that remains true to a large extent, we now know that in addition to NMDAR-dependent LTD, there are several other forms of LTD, which we will discuss in later sections. Moreover, similar to LTP, evidence is accumulating that LTD mechanisms may contribute to a large number of brain phenomena including experience-dependent development, learning and memory, addiction, and neurological disorders such as Alzheimer's disease and Parkinson's disease (Malenka and Bear, 2004; Brebner *et al*, 2005; Kreitzer and Malenka 2007; Hsieh *et al*, 2006).

Triggering NMDAR-dependent LTD. The typical protocol for eliciting LTD involves prolonged repetitive low-frequency stimulation ($\sim$900 stimuli at 1 Hz; Dudek and Bear, 1992; Mulkey and Malenka, 1992), although the number of stimuli can be dramatically reduced and the frequency changed if the postsynaptic neuron is modestly depolarized (to ~ -50 mV), partially relieving the Mg^{2+} block of the NMDAR (Selig *et al*, 1995). NMDAR-dependent LTD can also be induced by correctly timing the activation of presynaptic axons and the postsynaptic neuron (STDP; (Dan and Poo, 2006).

Like LTP, LTD is input-specific and depends upon an NMDAR-dependent increase in postsynaptic calcium (Mulkey and Malenka, 1992). The predominant current hypothesis is that quantitative properties of the postsynaptic calcium signal within dendritic spines dictates whether LTP or LTD is triggered, with LTD requiring a modest increase in calcium (Cummings *et al*, 1996), whereas LTP requires a increase beyond some critical threshold value (Malenka and Nicoll, 1993). The temporal characteristics of the increase in calcium may also be important since changing the relative timing between pre- and postsynaptic activation by just a few tens of milliseconds can reverse the direction of synaptic modification (Dan and Poo, 2006). Differential buffering of postsynaptic calcium levels has been reported to enable a transition between LTP and LTD (Harney *et al*, 2006; Nishiyama *et al*, 2000). These findings demonstrate the thin line that lies between synaptic activity eliciting a potentiation *vs* a depression and provide support to the idea that both LTP and LTD are utilized in parallel for encoding experiences *in vivo*.

LTD signal transduction mechanisms. An influential hypothesis for the signal transduction pathway triggering LTD suggested that while LTP was due to the preferential activation of CaMKII, LTD involves activation of a calcium-dependent protein phosphatase cascade consisting of the calcium/calmodulin-dependent phosphatase calcineurin (also known as protein phosphatase 2B), PP1, and a phosphoprotein termed inhibitor-1 which functions to inhibit PP1 until it is dephosphorylated by calcineurin (Lisman, 1989). Consistent with this hypothesis, postsynaptic inhibition of these phosphatases prevents LTD (Kirkwood and Bear, 1994; Morishita *et al*, 2001; Mulkey *et al*, 1994, 1993), whereas directly loading CA1 pyramidal cells with PP1 enhances LTD (Morishita *et al*, 2001). Although signaling proteins other than phosphatases have been suggested to play key roles in LTD (Bolshakov *et al*, 2000; Dan and Poo, 2006; Palmer *et al*, 2005; Peineau *et al*, 2007), the hypothesis that LTP involves preferential activation of protein kinases while LTD involves activation of phosphatases remains predominant.

LTD has been found to correlate with dephosphorylation of postsynaptic PKC and PKA substrates without a detectable change in CaMKII substrate phosphorylation

(Hrabetova and Sacktor, 1996; Kameyama *et al*, 1998; Lee *et al*, 2000, 1998. The evidence in support of a role for dephosphorylation of PKA substrates during LTD is particularly convincing, as postsynaptic inhibition of PKA, or its displacement from intracellular anchoring proteins, cause a rundown of synaptic transmission that occludes LTD. The mechanism underlying specific dephosphorylation of PKA substrates during LTD could involve the NMDAR-dependent recruitment of PP1 to synapses (Morishita *et al*, 2001) or the selective loss of PKA from synapses (Gomez *et al*, 2002; Snyder *et al*, 2005). Consistent with a role for PKA, LTD is associated with selective dephosphorylation of Ser845 on GluR1, a PKA substrate site (Lee *et al*, 2000). This dephosphorylation event may contribute to the expression of LTD, as it decreases the AMPAR open-channel probability (Banke *et al*, 2000), and mice with knock-in alanine substitution of both Ser845 and Ser831 (a CaMKII-substrate site) exhibit impaired NMDAR-dependent LTD (Lee *et al*, 2003).

Expression mechanisms of LTD. The demonstration of silent synapses and their conversion to functional synapses during LTP by the incorporation of AMPARs (Malenka and Nicoll, 1997) immediately gave credence to the idea that the opposite might happen during LTD, that is, the removal or endocytosis of AMPARs. Consistent with this idea, it was demonstrated that pharmacological manipulations of activity in cultured neurons (Carroll *et al*, 1999; Lissin *et al*, 1998) or application of glutamate receptor agonists (Beattie *et al*, 2000; Carroll *et al*, 1999; Ehlers, 2000; Heynen *et al*, 2000; Lin *et al*, 2000; Lissin *et al*, 1998) could cause a loss of AMPARs from synapses due to dynamin- and clathrin-dependent endocytosis (Carroll *et al*, 2001; Collingridge *et al*, 2004; Derkach *et al*, 2007; Malinow and Malenka, 2002). Furthermore, postsynaptic inhibition of dynamin activity impaired LTD in CA1 pyramidal cells in slices (Lee *et al*, 2002; Luscher *et al*, 1999; Morishita *et al*, 2005). Based in large part on these sorts of observations, the current leading hypothesis is that the expression mechanism of NMDAR-dependent LTD is due to activity-dependent endocytosis of synaptic AMPARs (Bredt and Nicoll, 2003; Collingridge *et al*, 2004; Derkach *et al*, 2007; Malenka and Bear, 2004; Malinow and Malenka, 2002) (Figure 2).

The precise molecular mechanisms by which endocytosis of AMPARs occurs during LTD is still not clear but one likely scenario is that it involves dissociation of AMPARs from their anchors within the PSD, followed by lateral movement to the edge of the PSD where they undergo clathrin- and dynamin-dependent endocytosis (Ashby *et al*, 2004; Blanpied *et al*, 2002; Groc *et al*, 2004). Consistent with a key role for protein phosphatases, the endocytosis of AMPARs is regulated by calcium-dependent dephosphorylation (Beattie *et al*, 2000; Carroll *et al*, 2001; Ehlers, 2000). Key substrates for facilitating endocytosis may include components of the endocytic machinery (Carroll *et al*, 2001; Lai *et al*, 1999; Slepnev *et al*, 1998) as well as AMPAR subunits themselves (Ehlers, 2000). Following endocytosis, AMPARs exhibit increased colocalization with the clathrin adaptor protein AP2 (Carroll *et al*, 1999), an interaction that may be promoted by the Ca^{2+}-dependent adaptor protein hippocalcin (Palmer *et al*, 2005).

Consistent with a role for 'slot proteins' in the regulation of AMPAR surface levels, LTD has been reported to depend on PP1-dependent dephosphorylation of stargazin (Tomita *et al*, 2005b). This dephosphorylation might permit the dissociation of stargazin from PSD-95 and its diffusion out of the PSD, enabling LTD through loss of synaptic AMPARs (Ziff, 2007). Ubiquitination (Colledge *et al*, 2003) or depalmitoylation (El-Husseini *et al*, 2002) of PSD-95 has also been suggested to be critical for agonist-induced endocytosis of AMPARs but whether these events are required for synaptically induced LTD has not been determined. Additional proteins implicated in AMPAR endocytosis include the AMPAR interacting protein PICK1 (Hanley and Henley, 2005; Kim *et al*, 2001), the small GTPases Rap1 (Zhu *et al*, 2002, 2005) and Rab5 (Brown *et al*, 2005), and a protein termed cpg2 (Cottrell *et al*, 2004).

It has been suggested that particular AMPAR subunits, specifically GluR2, may be especially important for the endocytosis of AMPARs during LTD, in part because of its direct interaction with AP2 (Lee *et al*, 2002). One key finding consistent with this hypothesis is that peptides that selectively interfere with this interaction have been reported to inhibit LTD (Lee *et al*, 2002). However, AP2 can bind other AMPAR subunits (Kastning *et al*, 2007; Lee *et al*, 2002) and LTD is still observed in hippocampal slices obtained from mice lacking GluR2 as well as GluR2 and GluR3 (Jia *et al*, 1996; Meng *et al*, 2003). Thus, the importance of specific AMPAR subunits for LTD is not firmly established.

Summary. A current simplified view of the mechanisms underlying NMDAR-dependent LTD can be summarized as follows (Figure 2): a modest increase in postsynaptic calcium concentration within dendritic spines due to modest activation of NMDARs leads to preferential activation of protein phosphatases (as well as a few other key signaling proteins). This leads to the dissociation of AMPARs from their molecular scaffolds in the PSD and their lateral movement to endocytic zones on the periphery of the PSD, where they are endocytosed and potentially degraded. We have not discussed the maintenance of LTD because there is little work on this topic. There is evidence that LTD is accompanied by a shrinkage in the size of dendritic spines (Nagerl *et al*, 2004; Zhou *et al*, 2004) and that this may be due to the loss of AMPARs (Hsieh *et al*, 2006). Furthermore, similar to LTP, protein translation may be needed for the long-term stable expression of LTD (Pfeiffer and Huber, 2006). Thus, it is generally believed that the activity-dependent trafficking of AMPARs into and out of synapses during LTP and LTD, respectively, is the first critical step in the morphological growth or shrinkage of synapses and that these structural modifications are the mechanisms by which bidirectional changes in synaptic strength are maintained. Indeed, the size of individual synapses correlates closely with the number of AMPARs they contain (Matsuzaki *et al*, 2001; Nusser *et al*, 1998; Takumi *et al*, 1999).

Presynaptic LTP

Although the spotlight has been on NMDAR-dependent LTP for over 30 years, it is clear that a mechanistically distinct

form of plasticity coexists in the hippocampus at the so-called mossy fiber synapses, the synapses between the axons of dentate gyrus granule cells (ie, mossy fibers) and the proximal apical dendrites of CA3 pyramidal cells (Nicoll and Malenka, 1995; Nicoll and Schmitz, 2005). Mossy fiber LTP (MF-LTP) is of increasing interest due to the fact that it appears to be a prototype for mechanistically similar forms of LTP found in several other brain regions including the thalamus at corticothalamic synapses (Castro-Alamancos and Calcagnotto, 1999), the cerebellum at parallel fiber-Purkinje cell synapses (Linden, 1997; Salin *et al*, 1996), and perhaps in the striatum at cortico-striatal synapses (Spencer and Murphy, 2002). Thus, like NMDAR-dependent LTP, this form of LTP may play multiple functional roles in the brain.

In contrast to NMDAR-dependent LTP, the triggering and expression of this form of LTP is thought to be solely or predominantly presynaptic, thus we refer to it as presynaptic LTP. While somewhat controversial, most experimental evidence suggests that presynaptic LTP is triggered by high-frequency tetanic stimulation, which causes a large, activity-dependent increase in calcium concentration within presynaptic axon terminals (Nicoll and Malenka, 1995; Nicoll and Schmitz, 2005; Zalutsky and Nicoll, 1990). Presynaptic voltage-dependent calcium channels are the critical source of the calcium increase, although the triggering of this LTP at MF synapses can be facilitated by the activation of presynaptic kainate receptors, particularly GluR6 (Lauri *et al*, 2001; Schmitz *et al*, 2003). Results from pharmacological manipulations and knockout mice are all consistent with the hypothesis that the increase in presynaptic calcium activates a calcium/calmodulin-dependent adenylyl cyclase. This leads to a increase in presynaptic cAMP and activation of PKA, which phosphorylates critical presynaptic substrates to cause a long-lasting enhancement in transmitter release (Nicoll and Malenka, 1995; Nicoll and Schmitz, 2005). Although this sequence of events is consistent with most of the results from all of the synapses that have been reported to express presynaptic LTP, surprisingly, a very different postsynaptic induction mechanism has been proposed to occur at MF synapses. This involves trans-synaptic interactions between postsynaptic EphB receptor tyrosine kinases and presynaptic B-Ephrin ligands leading, via an unknown mechanism, to a long-lasting enhancement of transmitter release (Armstrong *et al*, 2006; Contractor *et al*, 2002).

Despite some controversy concerning the mechanism underlying the induction of presynaptic LTP at MF synapses, there is general agreement that its expression is due to an increase in neurotransmitter release. One mechanism for mediating a long-lasting increase in transmitter release is to enhance the calcium influx into the presynaptic terminal when it is invaded by an action potential; for example via a long-lasting modulation of presynaptic calcium channels. However, direct imaging of the action potential-dependent increase in presynaptic calcium in MF boutons indicates that no change occurs following the triggering of MF-LTP (Kamiya *et al*, 2002; Regehr and Tank, 1991; Reid *et al*, 2004).

The other major mechanism for enhancing transmitter release is via some modulation of the machinery responsible for synaptic vesicle exocytosis. In this context, the focus has been on presynaptic proteins known to be substrates for PKA. Because presynaptic terminals are relatively inaccessible, an important approach has been examining knockout mice lacking specific presynaptic proteins. Mice lacking synapsins exhibited normal MF-LTP (Spillane *et al*, 1995) indicating that these prominent PKA substrates were not necessary. In contrast, knockout animals lacking the synaptic vesicle protein Rab3A, a small GTPase (Castillo *et al*, 1997; Lonart *et al*, 1998), or its binding partner, the active zone protein Rim1α (Castillo *et al*, 2002; Powell *et al*, 2004) lack both MF-LTP as well as presynaptic LTP in the cerebellum. Rim1α is a substrate of PKA and thus these findings suggest that presynaptic LTP may require a GTP-dependent interaction between Rab3a and Rim1α at the interface of synaptic vesicles and the active zone. Indeed, using cultures of cerebellar neurons in which presynaptic LTP can be elicited, the critical residue phosphorylated by PKA in Rim1α has been identified (Lonart *et al*, 2003). One important caveat to this hypothesis, however, is that the presynaptic enhancement of synaptic transmission seen upon application of the adenylyl cyclase activator forskolin is unaltered in knockout mice lacking Rab3a or Rim1α. This provides a complication for the simple model implicating Rim1α and Rab3a as the crucial mediators of the enhanced transmission caused by presynaptic activation of PKA.

Metabotropic Glutamate Receptor-Dependent LTD

Under the appropriate experimental conditions, low-frequency stimulation of the Schaffer collateral/commissural inputs to CA1 pyramidal cells can trigger, in addition to NMDAR-dependent LTD, a mechanistically distinct form of LTD, that is dependent upon activation of metabotropic glutamate receptors (mGluRs; mGLUR LTD) (Anwyl, 2006; Bolshakov *et al*, 2000; Malenka and Bear, 2004; Oliet *et al*, 1997). Various forms of mGluR LTD have been observed in many brain regions, most notably at the parallel fiber to Purkinje cell synapse (Ito, 1989; Linden and Connor, 1995). This so-called cerebellar LTD is elicited when parallel fibers are activated coincident with climbing fiber activation and has been suggested to be particularly important for certain forms of motor learning.

Typically, the induction of mGluR LTD in the CA1 region of the hippocampus requires bursts of afferent stimulation or paired-pulse stimulation at modest frequencies. Presumably, this increases the likelihood of activating the extrasynaptic group I mGluRs that are required to trigger this form of plasticity. mGluR LTD can also be elicited by bath application of group I mGluR agonists such as DHPG (Bellone and Luscher, 2005; Huber *et al*, 2000, 2001). Group I mGluRs (mGluR1 and mGluR5) are defined by their capacity to stimulate phosphoinositide hydrolysis and thereby produce diacylglycerol and inositol triphosphate. Although mGluR1 is the principal receptor implicated in the induction of mGluR LTD in the ventral tegmental area (VTA), cerebellum, and neostriatum, mGluR5 has been implicated in the hippocampus, cortex, and nucleus accumbens (Anwyl, 2006).

The intracellular signaling pathways responsible for mGluR LTD have not been extensively examined. PKC appears to be required for mGluR LTD in the cerebellum

(De Zeeuw *et al*, 1998; Linden and Connor, 1991) and the VTA (Bellone and Luscher, 2005), but perhaps not in the hippocampus (Huang and Hsu, 2006). Other signaling proteins suggested to be important for mGluR LTD include the MAPKs p38, Erk, and Jnk (Gallagher *et al*, 2004; Li *et al*, 2007; Rush *et al*, 2002), tyrosine phosphatases (Huang and Hsu, 2006; Moult *et al*, 2006), and phosphatidylinositol 3-kinase (Hou and Klann, 2004) but how these various enzymes might lead to a long-lasting decrease in synaptic strength is unknown.

Similar to NMDAR-dependent LTD, mGluR LTD in the hippocampus and cerebellum appears to involve clathrin-dependent endocytosis of AMPARs (Snyder *et al*, 2001; Wang and Linden, 2000; Xiao *et al*, 2001). For cerebellar mGluR LTD, a large body of work is consistent with a specific molecular model in which mGluR activation due to parallel fiber stimulation combined with calcium influx due to climbing fiber activation results in activation of PKCα and its targeting to synapses via the protein PICK1 (Jorntell and Hansel, 2006; Perez *et al*, 2001; Steinberg *et al*, 2006). PKCα then phosphorylates Ser880 on GluR2 causing GluR2 to dissociate from the AMPAR-binding proteins GRIP/ABP and bind to PICK1. This then allows lateral diffusion of the AMPARs and ultimately internalization (Chung *et al*, 2003; Steinberg *et al*, 2006; Xia *et al*, 2000). This cascade of events is significantly different than those believed to occur during NMDAR-dependent LTD, pointing out that the molecular mechanisms underlying apparently similar forms of plasticity may be cell type-specific. Indeed, mGluR LTD at excitatory synapses onto dopamine cells in the VTA has been suggested to involve a selective loss of AMPARs that lack the GluR2 subunit (Bellone and Luscher, 2005, 2006), rather than those that contain GluR2.

Another important feature of mGluR LTD, at least in the hippocampus, is that it appears to be dependent on mGluR-triggered protein synthesis (Hou and Klann, 2004; Huber *et al*, 2000, 2001; Snyder *et al*, 2001). This link between protein synthesis and mGluR LTD gained considerable attention following the report that mice lacking the gene encoding the fragile X mental retardation protein (FMRP) exhibited enhanced mGluR LTD in both the hippocampus (Huber *et al*, 2002) and the cerebellum (Koekkoek *et al*, 2005). These mice serve as a model for the Fragile X syndrome in humans, an X-linked form of mental retardation, and exhibit several features of the human disorder (Bear *et al*, 2004). Surprisingly, the enhanced mGluR LTD observed in the FMRP knockout mice is independent of protein synthesis and proteasomal degradation (Hou *et al*, 2006; Nosyreva and Huber, 2006), cellular processes that appear crucial for mGluR LTD in wild-type mice. Nevertheless, this potential link between an mGluR-triggered form of synaptic plasticity and Fragile X syndrome has focused attention on mGluR antagonists as possible therapeutic agents for this and other developemental disorders (Bear *et al*, 2004).

There are also results consistent with a presynaptic locus of expression for mGluR LTD (Anwyl, 2006; Nosyreva and Huber, 2005; Zakharenko *et al*, 2002). As these forms of mGluR LTD are still triggered postsynaptically, they must involve a retrograde messenger, one leading candidate being 12-lipoxygenase metabolites of arachidonic acid (Feinmark *et al*, 2003). In an attempt to reconcile the observations of a presynaptic locus of expression of mGluR LTD with the bulk of the literature describing a postsynaptic locus of expression, a developmental shift in the mechanisms of mGluR LTD has been proposed (Nosyreva and Huber, 2005). Specifically, it has been suggested that in slices prepared from neonatal (P8–P15) animals, mGluR-LTD is independent of protein synthesis and is due to a presynaptic modification, whereas in older animals (P21–P35) mGluR LTD is mediated by a protein synthesis-dependent reduction in the postsynaptic levels of AMPARs.

Endocannabinoid-Mediated LTD

A major advance over the last decade has been the demonstration of the existence of endogenous cannabinoids (termed endocannabinoids) and their roles in modulating synaptic function (Chevaleyre *et al*, 2006; Freund *et al*, 2003; Kreitzer and Regehr, 2002; Piomelli, 2003; Wilson and Nicoll, 2002). It is now well established that in a number of brain regions endocannabinoids are retrograde messengers that are released by postsynaptic cells in response to strong depolarization and/or activation of G-protein-coupled receptors (eg, mGluRs and muscarinic receptors) and function to transiently inhibit transmitter release (for $\sim$0.5–1 min) at either excitatory or inhibitory synpases via activation of presynaptic CB1 receptors.

Much of the mechanistic work on the transient synaptic effects of endocannabinioids was performed in the hippocampus and cerebellum, synapses that are often thought to be prototypic of synapses throughout the brain. It was therefore surprising when a form of LTD that required endocannabinoids, (so-called endocannabinoid-mediated LTD; eCB-LTD) was observed in the glutamatergic synapses onto medium spiny neurons in the striatum as well as at synapses between layer V pyramidal neurons (Gerdeman *et al*, 2002; Robbe *et al*, 2002a; Sjostrom *et al*, 2003). In the hippocampus, in contrast, endocannabinoids mediate a form of LTD at inhibitory, but not excitatory, synapses (Chevaleyre and Castillo, 2004). In the dorsal striatum, eCB-LTD requires postsynaptic activation of group I mGluRs, L-type calcium channels and D2 dopamine receptors (Choi and Lovinger, 1997; Kreitzer and Malenka, 2005, 2007; Pisani *et al*, 2005; Sung *et al*, 2001; Tang *et al*, 2001) (Figure 3). This leads to the production most likely of anandamide (Ade and Lovinger, 2007), which activates presynaptic CB1 receptors. However, prolonged activation of these CB1 receptors alone is not sufficient to elicit eCB-LTD; concomitant presynaptic activity is also required, a requirement that likely accounts for the input specificity of this form of plasticity (Singla *et al*, 2007). Another important feature of eCB-LTD in the dorsal striatum is that it appears to be restricted to the medium spiny neurons that primarily express D2 dopamine receptors and is not present at excitatory synapses on cells expressing D1 receptors (Kreitzer and Malenka, 2007; but see Wang *et al*, 2006). This cell-restricted expression of eCB-LTD may have important functional implications, a topic to be discussed below.

In the nucleus accumbens (NAc), eCB-LTD also requires postsynaptic activation of group I mGluRs and is modulated by drugs of abuse (Fourgeaud *et al*, 2004; Mato *et al*, 2004; Robbe *et al*, 2002b). In the cortex, eCB-LTD can be elicited

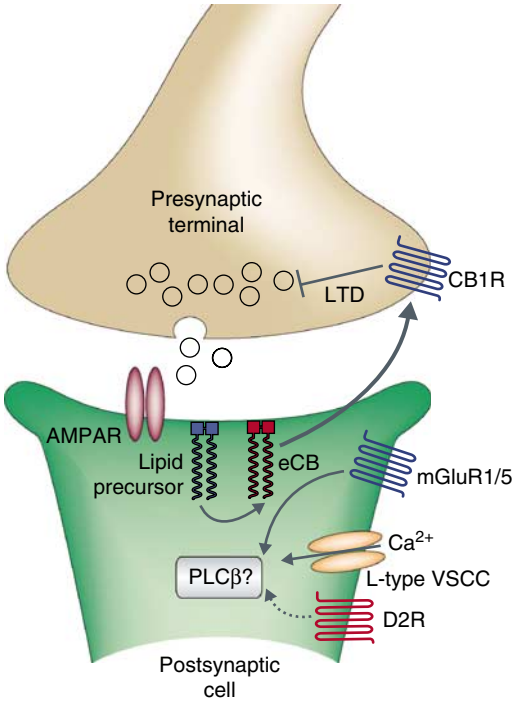

Figure 3 Model of eCB-LTD at excitatory synapses onto medium spiny neurons in the striatum. Activation of postsynaptic type I mGluRs, along with coincident subthreshold depolarization of medium spiny neurons sufficient to activate L-type voltage-sensitive calcium channels (VSCCs), stimulates the postsynaptic synthesis and release of endocannabinoids. What enzyme generates the endocannabinoids is not known; one candidate is PLCβ. Co-activation of postsynaptic dopamine D2-type receptors (D2R) enhances endocannabinoid production and the subsequent induction of presynaptic LTD, mediated through activation of presynaptic CB1 receptors (CB1R). (From Kreitzer and Malenka, 2005.)

by a spike-timing-dependent protocol (Sjostrom *et al*, 2003) but does not depend on postsynaptic activation of mGluRs and surprisingly, requires coincident activation of presynaptic NMDARs. LTD in the cerebellum was also reported to depend on retrograde endocannabinoid signaling (Safo and Regehr, 2005), but the mechanistic basis for this observation is still unclear, since, as discussed above, cerebellar LTD is expressed postsynaptically.

Metaplasticity

Metaplasticity refers to a higher-order form of synaptic plasticity in which synaptic activity, which by itself does not directly affect synaptic efficacy, leads to a persistent change in the direction or magnitude of subsequent activity-dependent synaptic plasticity. In other words, metaplasticity is the 'plasticity of plasticity' (Abraham and Bear, 1996; Bear *et al*, 1987). The best-studied examples of metaplasticity are those in which prior activity shifts the threshold for LTP and LTD induction. For example, in the hippocampus, repetitive activation of NMDARs in a manner that does not elicit LTP or LTD can nonetheless elicit a rapid shift in plasticity thresholds such that LTP becomes difficult to elicit and LTD induction is favored (Huang *et al*, 1992; Wang and Wagner, 1999). A potential functional role for metaplasticity has been demonstrated by modifying the level of activity during the development of the visual cortex *in vivo* (Philpot *et al*, 2001, 2003, 2007). This causes shifts in the thresholds for LTP and LTD in cells in visual cortex presumably due to changes in the stoichiometry of synaptic NMDARs. As discussed below, such changes in synaptic plasticity may importantly contribute to the experience-dependent plasticity of ocular dominance following manipulation of the visual environment.

Synaptic Scaling: A Form of Homeostatic Plasticity

Theoretically, without additional stabilizing mechanisms, activity-dependent forms of plasticity such as LTP and LTD could drive neural circuit activity towards epileptogenic excitation or complete quiescence. Synaptic scaling is considered a form of homeostatic plasticity that counters potentially maladaptive effects of long-term synapse-specific plasticity by globally affecting the transmission through all synapses on a given neuron (Turrigiano and Nelson, 2004). In terms of its basic properties and underlying mechanisms, this form of synaptic plasticity contrasts dramatically with the forms of LTP and LTD we have discussed thus far.

Synaptic scaling occurs when network activity is dramatically decreased or increased for prolonged ($> \sim 12$–24 h) periods of time. Decreased activity (due to blockade of synaptic transmission or spiking) causes an increase in the strength of all excitatory synapses onto excitatory neurons, whereas increased activity (generally induced by partially blocking inhibitory synapses) reduces the strength of all excitatory synapses (Turrigiano *et al*, 1998). Importantly, the relative strengths of individual synpases appear to be maintained even though global synaptic input is significantly altered.

Relatively little is known about the molecular mechanisms underlying synaptic scaling other than it involves changes in the number of AMPARs (and NMDARs) at individual synapses (Perez-Otano and Ehlers, 2005; Turrigiano and Nelson, 2004; Watt *et al*, 2000) and likely presynaptic changes as well (Burrone and Murthy, 2003; Burrone *et al*, 2002). Recently, evidence has been presented supporting a role for secreted factors in the induction of homeostatic plasticity, suggesting that key triggers for this form of plasticity may not be cell autonomous. Specifically, secretion of the proinflammatory cytokine tumor necrosis factor-α from glial cells appears to be necessary for the increase in the level of synaptic AMPARs caused by extended periods of activity blockade (Beattie *et al*, 2002; Stellwagen *et al*, 2005; Stellwagen and Malenka, 2006). In addition, there is evidence suggesting a role for secreted BDNF in driving the opposite form of synaptic scaling; the decrease in synaptic strengths caused by extended periods of increased network acitivity (Rutherford *et al*, 1998; Turrigiano, 2006).

FUNCTIONAL ROLES OF LTP AND LTD

Although LTP and LTD are prime candidate mechanisms underlying many different forms of experience-dependent plasticity, it is important to remember that they are experimental phenomena used to examine how different

patterns of activity can elicit bidirectional control over synaptic strength. Establishing a causal connection between a specific form of synaptic plasticity and the behavioral consequences of specific experiences remains a daunting task. Nevertheless, over the last decade, significant advances have been made in connecting synaptic plasticity to a number of different types of adaptive experience-dependent plasticity. Furthermore, it has become increasingly clear that understanding the mechanisms of synaptic plasticity may provide important insights into the pathophysiology of a variety of neuropsychiatric disorders and also point the way toward novel therapeutic approaches. In the following sections, we will briefly provide examples that demonstrate that LTP and LTD do occur *in vivo* in response to experience and may play a causal role in mediating the consequences of experience.

Hippocampal-Dependent Plasticity and Learning

Given that LTP was first described in the hippocampus, a structure well established to be critically important for declarative memory (Squire *et al*, 2004), it is not surprising that over the last three decades there has been a major effort aimed at demonstrating a role for hippocampal LTP in encoding new memories (Martin *et al*, 2000; Morris, 2006). Correlations have been observed between defective hippocampal synaptic plasticity and defective hippocampal-dependent memory tasks upon perturbation of a number of proteins which function in synaptic plasticity, either pharmacologically, or through gene knockout (Lynch, 2004; Martin *et al*, 2000; Morris, 2006). For example, rodents in which NMDAR antagonists were infused into the hippocampus (Morris and Frey, 1997), as well as mice lacking expression of the NMDAR subunit NR1 in the forebrain (Tsien *et al*, 1996), are defective both in LTP and certain types of spatial learning. Furthermore, mice in which the specific NMDAR subunit NR2B was overexpressed to enhance NMDAR function were reported to display enhanced LTP and enhanced spatial learning (Tang *et al*, 1999). Recently, more compelling evidence for a role of synaptic plasticity in hippocampal-dependent learning has been presented. During an inhibitory avoidance task, LTP could be recorded *in vivo* in a subset of hippocampal CA1 pyramidal cells (Whitlock *et al*, 2006). This demonstrated that the patterns of activity generated during a real learning task were sufficient to elicit LTP. Perhaps even more convincing was the demonstration that *in vivo* infusion of a PKMζ inhibitor into the hippocampus abolished the maintenance of LTP and simultaneously the storage of a long-lasting spatial memory (Pastalkova *et al*, 2006). These findings strongly suggest that maintained LTP was required for the engram that stored the key spatial information.

In addition to its role as a key component of the mechanisms underlying the encoding of declarative memories, hippocampal NMDAR-dependent LTP (as well as LTD) may provide important insights into the pathophysiology and potential treatment of major mental illnesses. For example, a leading hypothesis for the pathophysiology of schizophrenia posits a dysfunction in glutamatergic synapses, in particular a hypofunction of NMDARs (Coyle and Tsai, 2004; Javitt, 2006; McCullumsmith *et al*, 2004; Tamminga, 1998). Thus, understanding the signaling events downstream of NMDAR activation may provide important insights into this devastating disease. A role for dysfunctions in LTP and/or LTD mechanisms as possible contributors to schizophrenia is also attractive in that schizophrenia likely involves neurodevelopmental abnormalities (Lewis and Levitt, 2002) and these phenomena play an important role in the early postnatal development of neural circuitry (see below). Indeed, genetic variation in calcineurin, which is thought to play an important role in NMDAR-dependent LTD, has been associated with schizophrenia (Gerber *et al*, 2003).

Another example of the potential importance of studying LTP and LTD comes from investigation into the therapeutic mechanisms of drugs used to treat bipolar disorder. Drugs such as lithium, valproate, and lamotrigine have been reported to have significant effects on the phosphorylation of AMPAR subunits and affect their surface expression (Du *et al*, 2003, 2004, 2007; Gray *et al*, 2003). These findings suggest that these drugs may somehow tap into the same mechanisms that have evolved to generate LTP and LTD and also point to novel approaches for the development of new therapeutic agents that may prove efficacious for treatment of this illness.

Experience-Dependent Plasticity in the Developing Sensory Cortex

Sensory receptive fields in the cortex are modified by early postnatal experience and the link between synaptic plasticity and these forms of experience-dependent plasticity in sensory systems is becoming increasingly established (Foeller and Feldman, 2004; Karmarkar and Dan, 2006; Malenka and Bear, 2004). For example, a strong connection between synaptic plasticity and experience-dependent plasticity has been established in the visual system during the shift in ocular dominance caused by monocular deprivation (MD) (Foeller and Feldman, 2004; Karmarkar and Dan, 2006; Malenka and Bear, 2004). MD induces biochemical changes in AMPAR subunits in visual cortex that appear identical to those elicited during NMDAR-dependent LTD (Heynen *et al*, 2003) and visual cortical slices obtained from monocularly deprived animals show greatly reduced LTD (Crozier *et al*, 2007; Heynen *et al*, 2003), suggesting that LTD was elicited *in vivo*. Furthermore, *in vivo* recordings demonstrated that MD caused a rapid decrease in the visually evoked potential (VEP) from the deprived eye and a slower enhancement of the VEP from the open eye (Frenkel and Bear, 2004). Importantly, completely blocking activity in the deprived eye prevented the depression of the VEP demonstrating that this depression required retinal activity and, like LTD, was therefore activity-dependent (Frenkel and Bear, 2004).

Similar results have been obtained in somatosensory barrel cortex in that sensory deprivation by whisker trimming or plucking causes a weakening of synaptic responses in layer 2/3 cells and an occlusion of LTD (Allen *et al*, 2003). This appears to be due to alterations in the patterns of pre- and postsynaptic spiking *in vivo* in a manner that is ideal for generating spike-timing-dependent LTD (Celikel *et al*, 2004). LTP mechanisms, on the other hand, appear to be important for the strengthening of synapses in developing barrel cortex due to early postnatal

experience. *In vivo* experience drives recombinant GluR1 into barrel cortex synapses in a manner similar to that which occurs during NMDAR-dependent LTP, whereas expression of a short peptide that inhibits delivery of endogenous AMPARs blocks the experience-dependent increase in synaptic strength (Takahashi *et al*, 2003) as does a dominant-negative form of the synaptic scaffold protein PSD-95 (Ehrlich and Malinow, 2004). Thus, as predicted by theoretical considerations (Bienenstock *et al*, 1982; Stent, 1973), LTP and LTD mechanisms appear to be critically involved in early neural circuit development and it is not difficult to imagine how disruption in these mechanisms might contribute to a host of neurodevelopemental disorders such as autism (Geschwind and Levitt, 2007; Rubenstein and Merzenich, 2003).

Synaptic Plasticity and Fear Conditioning

Pavlovian fear conditioning is a form of associative memory that depends on the amygdala for its induction and maintenance (Sigurdsson *et al*, 2007). It occurs when a neutral stimulus (such as a tone) is temporally paired with a strong noxious stimulus (such as an electric shock) creating a memory trace, the consequences of which are that the neutral stimulus elicits the learned fear response. Considerable evidence is consistent with the hypothesis that LTP at sensory inputs to the lateral nucleus of the amygdala is necessary and perhaps sufficient for establishing this engram (Sigurdsson *et al*, 2007). NMDAR-dependent LTP can be induced at cortical and thalamic inputs into the lateral amygdala, both *in vitro* and *in vivo*. Importantly, fear conditioning induces synaptic potentiation at these synapses, and this increase in synaptic strength occludes further induction of LTP (McKernan and Shinnick-Gallagher, 1997; Rogan *et al*, 1997; Tsvetkov *et al*, 2002). Like NMDAR-dependent LTP in the hippocampus, fear conditioning has also been shown to lead to the insertion of new AMPARs at thalamic input synapses onto lateral amygdala neurons (Rumpel *et al*, 2005) and perhaps most convincingly, expression of a peptide that prevents the LTP-induced incorporation of AMPARs at synapses abolished acquisition of this form of associative memory (Rumpel *et al*, 2005).

NMDARs in the amgydala are also involved in the extinction of learned fear, which can be conceptualized as a different form of learning (Myers and Davis, 2002). Furthermore, acute treatment with D-cycloserine, a partial agonist of NMDARs, enhances the learning processes that are responsible for fear extinction via actions in the amygdala (Walker *et al*, 2002). On the basis of these observations, clinical trials have been initiated using D-cycloserine in combination with behavioral therapy to enhance the extinction of fear in phobic patients (Hofmann *et al*, 2006; Otto *et al*, 2007; Ressler *et al*, 2004). Results to date suggest that the administration of D-cycloserine either before or shortly after exposure to fearful cues does in fact enhance the extinction of the anxiety previously associated with specific cues. Thus, the study of the neural substrates of learned fear and its extinction is a compelling example of how research on the mechanisms of synaptic plasticity has directly led to a potential novel treatment for common psychiatric disorders.

Synaptic Plasticity in Dopamine Circuits

The defining characteristic of drug addiction is persistent and compulsive seeking and ingestion of drugs despite adverse consequences. Over the last decade, a leading hypothesis has been that an important neural substrate of addiction, in particular relapse, is long-term associative memory processes occurring in several neural circuits that receive input from midbrain dopamine neurons (Everitt and Robbins, 2005; Hyman *et al*, 2006). In other words, it is thought that addictive drugs can usurp the normal adaptive mechanisms underlying reward-based learning.

The most well-established key site of action of addictive drugs is the mesolimbic dopamine system consisting of the VTA and the NAc. Excitatory synaptic transmission in these structures is critical for mediating several forms of long-lasting, drug-induced behavioral plasticity (Everitt and Wolf, 2002; Hyman and Malenka, 2001). It, therefore, has been reasonable to hypothesize that plasticity at these synapses plays an important role in mediating some of the behavioral consequences of exposure to drugs of abuse (Wolf, 1998).

Indeed, it is now established that various forms of LTP and LTD can be elicited at excitatory synapses in the VTA and NAc (Gerdeman *et al*, 2003; Kauer, 2004; Kelley, 2004; Thomas and Malenka, 2003). Furthermore, administration of a single dose of several different classes of drugs of abuse causes a significant increase in synaptic strength at excitatory synapses onto dopamine cells in the VTA (Faleiro *et al*, 2004; Saal *et al*, 2003; Ungless *et al*, 2001). This increase shares mechanisms with LTP in the VTA and appears to involve upregulation of AMPARs (Ungless *et al*, 2001). This drug-induced 'LTP' appears to play a functional role in triggering or mediating some drug-induced behavioral adaptations, as both conditioned place preference and behavioral sensitization are blocked by injection of glutamate receptor antagonists into the VTA (Harris and Aston-Jones, 2003; Vanderschuren and Kalivas, 2000). In addition, conditioned place preference, as well as the synaptic potentiation that is observed following cocaine administration, are impaired in GluR1 knockout mice (Dong *et al*, 2004), with the caveat that these mice still exhibit robust behavioral sensitization in response to repeated exposure to psychostimulants (Dong *et al*, 2004; Vekovischeva *et al*, 2001).

While drugs of abuse have been observed to induce LTP in the VTA, LTD has been observed in the NAc following chronic *in vivo* cocaine administration (Thomas *et al*, 2001). Consistent with a functional role for this LTD in addiction, injection of glutamate receptor antagonists into the NAc abolishes the expression of behavioral sensitization (Kelley, 2004). Furthermore, amphetamine-induced behavioral sensitization and LTD in the NAc were both abolished by injection into the NAc of inhibitors of AMPAR endocytosis (Brebner *et al*, 2005). Interestingly, overexpression of GluR1 in the NAc (mimicking an 'LTP'-like condition) facilitates the extinction of cocaine-seeking (Sutton *et al*, 2003) and even makes cocaine aversive in a conditioned place preference assay (Kelz *et al*, 1999). Recently, it has also been reported that cocaine self-administration abolishes the ability to induce LTD in the

core of the NAc after prolonged (21 days) abstinence (Martin *et al*, 2006) and *in vivo* administration of tetrahydrocannabinol (THC) or cocaine impairs the generation of eCB-LTD (Fourgeaud *et al*, 2004; Mato *et al*, 2004; Robbe *et al*, 2002b). Thus, drugs of abuse may elicit certain forms of synaptic plasticity in specific circuits while simultaneously impairing plasticity in other circuits.

Synaptic plasticity in the dorsal striatum has also been correlated with certain learned behaviors, in particular in motor control (Gubellini *et al*, 2004; Pisani *et al*, 2005). In this context, it is important to note that two independent striatal circuits are thought to exist, the so-called 'direct' and 'indirect' pathways, which subserve different functions in motor control (Bolam *et al*, 2000). Indirect pathway medium spiny neurons (MSNs) project to the lateral globus pallidus and primarily express D2 dopamine receptors while direct pathway MSNs project to the substantia nigra and express D1 dopamine receptors. As mentioned in the section on eCB-LTD, this form of plasticity is primarily restricted to the indirect pathway MSNs and is absent in Parkinson's disease models (Kreitzer and Malenka, 2007). However, in slices from dopamine-depleted animals, indirect pathway eCB-LTD can be rescued by a D2 receptor agonist or pharmacological inhibitors of endocannabinoid degradation. Remarkably, administration of these drugs together *in vivo* dramatically reduces Parkinsonian motor deficits suggesting that endocannabinoid-mediated depression of indirect pathway synapses has a critical role in motor control and may be a valuable target for therapy of striatal-based brain disorders (Kreitzer and Malenka, 2007). This works also points out the potential power of examining the mechanisms of synaptic plasticity and placing them in the context of the neural circuits in which they are found.

Future Directions

We have attempted to briefly review the enormous field of synaptic plasticity research in a concise and accessible manner so that by the end of this article, readers will have a reasonably up to date knowledge of current thinking about the mechanisms underlying the major forms of synaptic plasticity in the mammalian brain and a sense of what their *in vivo* functions might be. By necessity we have had to leave out important topics such as how synaptic activity modulates NMDAR-mediated synaptic responses (eg, Morishita *et al*, 2005), inhibitory synaptic responses (Chevaleyre *et al*, 2006), or the intrinsic excitability of neurons (Xu and Kang, 2005; Zhang and Linden, 2003), all of which will have profound effects on neural circuit function. Furthermore, several compelling examples that correlate long-term synaptic plasticity with experience-dependent modifications in behavior have been left out, such as the role of cerebellar LTD in motor learning (Boyden *et al*, 2004; Ito, 2002; Jorntell and Hansel, 2006).

This review should also make clear that while extensive progress has been made, much remains unknown. Even for the most established forms of plasticity, NMDAR-dependent LTP and LTD in the CA1 region of the hippocampus, we still know little about the details of the signal transduction pathways triggering these forms of plasticity and which specific proteins are being modified to cause the changes in synaptic efficacy. We also know little about the molecular mechanisms underlying the structural changes in synapses that seem to accompany LTP and LTD. With the accumulation of evidence demonstrating that long-term synaptic modifications do in fact play important roles in a host of adaptive brain functions, we believe there is strong justification to continue efforts toward establishing the detailed molecular basis of the various forms of synaptic plasticity. This is particularly important because, as we have tried to make clear, such knowledge is likely to have a major impact on our understanding and treatment of a wide range of brain disorders.

What direction do we envision the field taking in the near future? By definition, synaptic plasticity is an electrophysiological phenomenon. Only by recording synaptic responses can the investigator be sure that synaptic function has been modified. Until relatively recently, most electrophysiological studies depended on pharmacological manipulations of proteins, an approach that was aided by the use of genetically modified mice. Thus far, gene knockout experiments addressing the function of $\sim$200 genes have been reported and close to 80% of these report effects on synaptic transmission or plasticity (Grant, 2006). With the growing consensus that NMDAR-dependent LTP is primarily mediated by an increase in postsynaptic AMPARs, while LTD is associated with loss of AMPARs from the PSD, there also has been an increased contribution of cell biologists who have focused on the molecular mechanisms underlying the changes in the levels of postsynaptic receptors as well as the changes in synaptic structure that occur. Indeed, a close interdependence has emerged between electrophysiologists and cell biologists and this has dramatically impacted the field. Thus, electrophysiologists are increasingly making use of tools that enable overexpression, knockdown, and molecular replacement of target proteins both *in vitro* and *in vivo* (eg, Schluter *et al*, 2006). These advances are enabling a true molecular dissection of the mechanisms underlying plasticity of mammalian brain synapses.

Recent advances in high-throughput technologies, such as gene-chip microarrays for mRNA profiling and advanced mass spectrometry for identification of multiple proteins in a mixed population, have enabled the identification of the molecular components of many biological phenomena and contributed significantly to understanding their regulation. Furthermore, the recent advent of 'systems biology' has contributed a number of conceptual advances that enable clearer interpretation of the complex interaction networks observed in signal transduction cascades (Alon, 2006). These advances have so far only lightly impacted the field of synaptic plasticity (Pocklington *et al*, 2006), but we envision that they will have increasing influence in the near future, despite the technical difficulties that are encountered when trying to apply these approaches to the inherently complex preparations used in the study of synaptic plasticity.

What might we gain from such studies? A clearer picture of the molecules which participate in the processes underlying the different forms of synaptic plasticity, and the dynamics of their activation and interactions, would enable the formulation of much more sophisticated models of the events underlying the triggering, expression, and maintenance of specific forms of synaptic plasticity. This in turn would create a strong foundation for focused efforts aimed at identifying the central pathways mediating synaptic

plasticity and assaying their relevance to the phenomenon measured electrophysiologically.

By combining electrophysiological, molecular, cell biological and proteomic approaches, we envision that the next few decades will bring further clarification of the detailed molecular mechanisms underlying the major forms of synaptic plasticity that we have discussed in this review. The use of more sophisticated molecular and genetic manipulations, in particular, the development of mouse lines with highly restricted expression of transgenes that can be turned on or off with fine temporal control, will simultaneously facilitate the examination of the neural circuit basis of behavior. Together, we believe these approaches will allow sophisticated manipulation of synaptic plasticity mechanisms in highly restricted neural circuits and thereby greatly advance our understanding of how synaptic plasticity mediates both adaptive and pathological experience-dependent plasticity. Applying these same approaches to disease models should yield new insights into the molecular pathology of diseases of the synapse such as addiction, schizophrenia, and Alzheimer's diseases and also pave the way toward the development of novel and more efficacious treatments.

ACKNOWLEDGEMENTS

RM gratefully acknowledges support from NIMH, NIDA, NINDS, and NARSAD. AC acknowledges the support of the The International Human Frontier Science Program Organization. We apologize to those colleagues whose work was not cited because of the large scope of this review and severe space limitations.

DISCLOSURE/CONFLICT OF INTEREST

RM is on the board of scientific advisors for Merck Inc., Renovis Inc. and Seaside Therapeutics. These duties had no influence on the content of this article. AC has no disclosures or conflict of interest.

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