CHAPTER

18

Synaptic Plasticity

Ruth Heidelberger, Harel Shouval, Robert S. Zucker and John H. Byrne

INTRODUCTION

Chemical synapses, which mediate chemical synaptic transmission (Chapters 10, 15 and 16), are not static transmitters of information. Their effectiveness waxes and wanes depending upon factors such as the frequency of stimulation and prior activity (Martin et al., 2000; Zucker and Regehr, 2002). The ability of synapses to change their strength, called synaptic plasticity, is critical not only for regulating the flow of information within neuronal circuits, but also for learning and memory. In homosynaptic plasticity, the strength of a synapse is changed as a consequence of activity in that synapse, whereas in heterosynaptic plasticity, the strength of a synapse changes as a result of activity in a neuron or pathway extrinsic to that synapse. Both forms of plasticity can occur over a wide range of temporal domains. Short-term plasticity refers to changes in synaptic strength that persist for seconds to minutes. Long-term synaptic plasticity refers to changes in synaptic strength that persist for hours, days, even lifetimes. In this chapter, we consider the mechanisms that underlie short-term and long-term plasticity of chemical synapses. Electrical synapses and their plasticity are discussed in Chapter 9.

SHORT-TERM PLASTICITY

Short-term plasticity, which lasts from seconds to minutes, is bidirectional, and may result in either a temporary increase or decrease in synaptic transmission. These short-term changes allow for the dynamic regulation of neural information processing and for types of short-term memory. *Facilitation* refers to an increase in the strength of a synaptic connection, whereas *depression* refers to a decrease in the strength of a synaptic connection. This section first describes homosynaptic depression and facilitation.

Short-Term Homosynaptic Depression and Facilitation

In the simplest scenario, short-term homosynaptic plasticity is manifest as an activity-dependent change in the amplitude of a postsynaptic potential (PSP; see Chapter 16). At the synapse between a sensory neuron and motor neuron in the spinal cord (Fig. 18.1A), a single action potential in the sensory neuron gives rise to an excitatory postsynaptic potential (EPSP) in the motor neuron with a particular amplitude. If a second action potential is given shortly after the first, the second EPSP may be larger than the first (Fig 18.1B). This is known as paired-pulse facilitation. However, the second action potential may produce an EPSP that is reduced in amplitude relative to the first (Fig 18.1C). This is called paired-pulse depression.

Short-term changes in synaptic strength can also be induced by more complex stimulation paradigms. At most synapses, repetitive high-frequency stimulation (called a tetanus) is initially dominated by facilitation. This process builds to a steady state within about 1 s and decays equally rapidly when stimulation stops. Decay is measured by single test stimuli given at various intervals after a conditioning train. Facilitation can often be divided into two exponential phases, called its first and second components, and may reach appreciable levels (typically a doubling of PSP size) after a single action potential. At most synapses, a slower phase of increase in efficacy, which has a characteristic time constant of several seconds and is called *augmentation*, succeeds facilitation. Finally, with prolonged stimulation, some synapses display a third phase of growth in PSP amplitude that lasts minutes and is called *potentiation*.

Often, a phase of decreasing transmission, called synaptic depression, is superimposed on these processes. Synaptic depression often tends to overlap and obscure the augmentation and potentiation phases. When stimulation ceases, recovery from the various

From Molecules to Networks.
DOI: http://dx.doi.org/10.1016/B978-0-12-397179-1.00018-X

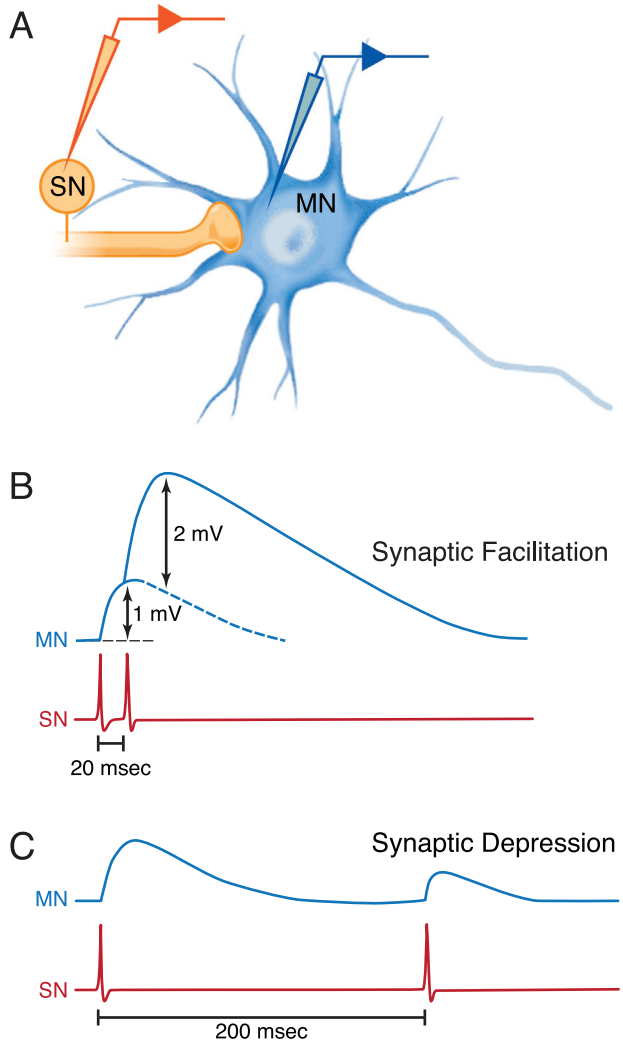

FIGURE 18.1 **Short-term homosynaptic plasticity at the synapse between a sensory afferent fiber (SN) and a spinal motor neuron (MN).** (A) Drawing of a SN-MN synapse. (B) Two action potentials in the presynaptic sensory afferent produce two EPSPs in the postsynaptic motor neuron. The first action potential produces a 1-mV EPSP, but the second action potential, which occurs about 20 ms after the first, produces an EPSP that is larger than the EPSP produced by the first. This is an example of paired-pulse facilitation. (C) When the second action potential in the sensory neuron is triggered 200 ms after the first, the corresponding EPSP is smaller than that produced by the first action potential. This is an example of paired-pulse depression.

processes occurs in the same order as their development during the tetanus, with facilitation decaying first, then depression and augmentation, and finally potentiation (Fig. 18.2). Thus, potentiation is often visible in isolation only long after a tetanus and is then called *posttetanic potentiation* (PTP). And, as discussed in a later section of this chapter, at some synapses, even longer-lasting effects (persisting for hours or more), named *long-term potentiation* (LTP) have been observed. In almost all synapses in which a quantal analysis has been performed, all these forms of

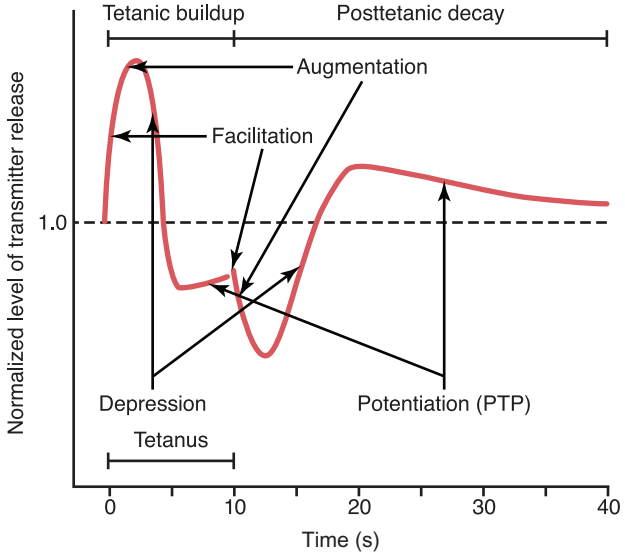

FIGURE 18.2 **Accumulation of the effects of facilitation, augmentation, depression, and potentiation on transmitter release** by each action potential in a tetanus (see horizontal bar), and the posttetanic decay of these phases of synaptic plasticity measured by single stimuli after the tetanus.

synaptic plasticity (except some forms of cortical LTP) are due to changes in the number of quanta released by action potentials. When binomial parameters were estimated (see Chapter 15), correlated changes in p and n were usually observed. This result is expected if release sites with nonuniform p become more effective while "silent" sites are recruited during enhanced transmission, and vice versa during depression.

Short-Term Homosynaptic Depression May Arise from Depletion of Readily Releasable Transmitter, or from a Variety of Other Processes

In contrast with the growth phases in short-term synaptic plasticity (discussed in the following), the rate at which short-term homosynaptic depression develops usually depends on stimulation frequency, whereas recovery from depression often proceeds with a single time constant of seconds to minutes in different preparations. At many synapses, depression is relieved when transmission is reduced by lowering $[Ca^{2+}]$ or raising $[Mg^{2+}]$ in the medium. These characteristics are consistent with depression being due to the depletion of a readily releasable pool (RRP) of docked and primed or nearly primed vesicles, and recovery being due to their replenishment from a supply store (Fig. 18.3) (Zucker, 1989); the styryl dye FM1-43 (see Chapter 15) has been used to differentially label reserve and readily releasable vesicle pools at *Drosophila* neuromuscular junctions (Kuromi and Kidokoro, 1998). The parameters of such a depletion model can be estimated

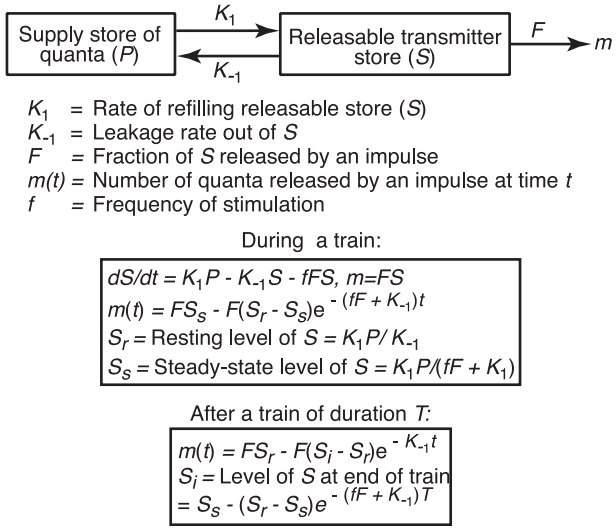

FIGURE 18.3 **The basic depletion model of synaptic depression.**

from the rate of recovery from depression, which gives the rate of refilling of the releasable store, and the fractional drop in PSPs given at short intervals, which gives the fraction of the releasable store liberated by each action potential. RRP size may be estimated from the accumulated release of rapidly depressing synapses, after accounting for replenishment of the RRP (Schneggenburger et al., 1999).

Recent data suggest that this basic depletion model is an oversimplification at many synapses. For example, as the RRP is depleted, both the probability of it releasing a vesicle (Dobrunz and Stevens, 1997; Wu and Borst, 1999) and its maximum capacity (Dobrunz and Stevens, 1997) appear to drop. More realistic models take account of the finite capacity of the RRP (Wu and Betz, 1998, Stevens and Wesseling, 1999). At the frog neuromuscular junction and hippocampal synapses, depression also involves a reduction in the rates of endocytotic vesicle recovery and of their transport into the RRP (Wu and Betz, 1998; Granseth and Lagnado, 2008). At other synapses, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) phosphorylation of synapsins mobilizes vesicles to the active zone by releasing them from tethering to actin filaments (Dittman and Regehr, 1998; Stevens and Wesseling, 1998; Wang and Kaczmarek, 1998; Sakaba and Neher, 2001; Sun et al., 2006). This leads to an activity-dependent acceleration of the rate of replenishing the RRP. Moreover, synaptic depression can occur at heterogenous rates at different synapses from a single neuron, likely due to variation in RRP size and mobilization rate (Sun et al., 2005), both of which are under regulation by munc18 (Toonen et al., 2006). Each of these details leads to departures from the predictions of the simple depletion model of Fig. 18.3.

Although depletion of vesicles is a mechanism for synaptic depression at some synapses, it cannot account for all forms of synaptic depression. At some synapses, depression is due to a feedback inhibitory action of released transmitter on presynaptic receptors called *autoreceptors*. For example, in rat hippocampal cortex, depression of GABA responses is blocked by antagonists of presynaptic $GABA_B$ receptors (Davies et al., 1990). At other synapses, such as those made by dorsal root ganglion neurons and by some brainstem neurons, depression is due partly to inactivation of Ca^{2+} channels during repetitive activity (Jia and Nelson, 1986; Xu and Wu, 2005); this mechanism, however, has been specifically rejected at other synapses (Charlton et al., 1982). Moreover, in a variety of central synapses in vertebrates and in the sea slug *Aplysia*, depression is due in part to desensitization of postsynaptic cholinergic and AMPA or NMDA glutamate receptors (Wachtel and Kandel, 1971; Mennerick and Zorumski, 1996; Otis et al., 1996). At *Aplysia* sensorimotor synapses, depression arises from a combination of desensitization, depletion of the RRP and release-independent inactivation of release sites (Gover et al., 2002; Royer et al., 2000; Zhao and Klein, 2002; Antzoulatos et al., 2003; Malkinson and Spira, 2013) that can be reactivated by high-frequency activity and cAMP-dependent protein kinase phosphorylation of synapsin. In contrast, a brief phase of depression has been attributed to a release-dependent refractoriness of release sites (Dobrunz et al., 1997; Zucker and Regehr, 2002; Neher and Sakaba, 2008; Pan and Zucker, 2009). Finally, a component of depression at hippocampal synapses is due to a drop in quantal size, apparently reflecting reduced presynaptic filling or partial or slow vesicle fusion (Chen et al., 2004).

Facilitation, Augmentation, and Potentiation are Due to Effects of Residual Ca^{2+}

With few exceptions (Wojtowicz and Atwood, 1988), all the phases of short-term enhancement of synaptic transmission are Ca^{2+} dependent in the sense that little or no facilitation, augmentation, or potentiation is generated by stimulation in Ca^{2+}-free medium. Originally, these phases of increased transmission were thought to be due to the summation of residual Ca^{2+} remaining in active zones after presynaptic activity with Ca^{2+} influx during subsequent action potentials to generate slightly higher peaks of $[Ca^{2+}]$ (Katz and Miledi, 1968; Zucker, 1989). Owing to the highly nonlinear dependence of transmitter release on $[Ca^{2+}]$, a small residual $[Ca^{2+}]$ could activate a substantial increase in phasic transmitter release during an action potential while simultaneously increasing miniature postsynaptic potential (mPSP) frequency. Temporal correlations between increased spike-evoked transmission after single action potentials or tetani and increases in mPSP

frequency supported this idea. But the tetanic accumulation of facilitation, augmentation, and potentiation did not accord quantitatively with predictions of a model of the accumulation of Ca^{2+} acting at one site (Magleby and Zengel, 1982). Simulations of expected levels of peak and residual Ca^{2+} levels also were unable to account for the full magnitude of facilitation (Yamada and Zucker, 1992). Presynaptic [Ca^{2+}] measurements confirmed the persistence of residual Ca^{2+} after repetitive stimulation during facilitation, augmentation, and PTP, but showed that it was too weak to explain augmentation or potentiation by simply summating with peak [Ca^{2+}] from Ca^{2+} channels at release sites (Delaney et al., 1989; Delaney and Tank, 1994; Atluri and Regehr, 1996). These findings led to the proposal that, in addition to summating with peak [Ca^{2+}] transients at release sites, residual Ca^{2+} acts to increase transmission at one or more targets that are distinct from sites that trigger exocytosis.

Two possibilities exist. Residual free Ca^{2+} could act in rapid equilibrium with such sites to increase transmission (Matveev et al., 2002), in which case the kinetics of enhanced release would mirror those of residual Ca^{2+}. Alternatively, Ca^{2+} could bind to these targets and activate processes that increase release after residual Ca^{2+} has dissipated (Yamada and Zucker, 1992). The latter idea is suggested by experiments in which facilitation, augmentation, or potentiation persists when residual Ca^{2+} should be absorbed by presynaptic introduction of exogenous chelators; however, results of this sort of experiment have not been consistent (Zucker, 1994). The former idea is supported by experiments in which photolabile BAPTA derivatives were injected presynaptically at crayfish neuromuscular junctions (Kamiya and Zucker, 1994). Posttetanic photolysis to produce enough chelator to suddenly remove residual Ca^{2+} after conditioning stimulation sharply reduced facilitation within a few milliseconds, and it reduced augmentation and potentiation within about 1 s. These results suggest that Ca^{2+} can "prime" subsequent phasic release by action potentials by acting at two additional targets distinct from the exocytosis trigger: a fast site responsible for facilitation and a slow one for augmentation and potentiation.

There are numerous additional indications of separate sites of Ca^{2+} action in short-term synaptic plasticity:

1. Very low temperatures caused facilitation to grow while secretion decayed after one action potential at frog neuromuscular junctions (Van Der Kloot, 1994).
2. Sr^{2+} and Ba^{2+}, divalent cations that can substitute for Ca^{2+} in some reactions, selectively enhance facilitation and augmentation, respectively, of both evoked transmitter release and miniature end-plate potential frequency at frog neuromuscular junctions (Zengel and Magleby, 1980; Zengel and Magleby, 1981). This could, however, also be explained by these ions being handled differently by intracellular buffers and removal processes.
3. Facilitation, augmentation, and potentiation are approximately linearly related to residual $[Ca^{2+}]_i$, whereas secretion involves a high degree of Ca^{2+} cooperativity (Delaney and Tank, 1994; Wright et al., 1996; Vyshedskiy and Lin, 1997; Korogod et al., 2005).
4. Ca^{2+} may enter terminals via private routes (e.g., through L-type Ca^{2+} channels or presynaptic kainate autoreceptors) to activate facilitation without directly triggering release (Jensen et al., 1999; Sun and Dobrunz, 2006).
5. Some synapses have an extremely low basal probability of vesicular release to an action potential, which grows dramatically during repetitive activity. At such strongly facilitating synapses, vesicles that are releasable in a train (the RRP) are not all immediately releasable, but must first undergo a final Ca^{2+}-dependent "priming" step (Millar et al., 2005).
6. Facilitation can have widely different magnitudes at different synapses from a single neuron; apparently it is independently regulable (Bittner, 1968; Pelkey and McBain, 2007).
7. *Drosophila* mutants defective in enzymes affecting cAMP-dependent phosphorylation show reduced facilitation and potentiation (Zhong and Wu, 1991). Transformed *Drosophila* carrying an inhibitor of CaMKII have impaired facilitation, augmentation, and potentiation (Wang et al., 1994). PTP of peptidergic release is induced by the mobilization of reserve dense core vesicles and their capture at release sites by activation of CaMKII by Ca^{2+} released from the endoplasmic reticulum via Ca^{2+}-induced Ca^{2+} release (Levitan, 2008; Wong et al., 2009).
8. Mice lacking synapsin I and/or synapsin II show specific defects in facilitation and potentiation in hippocampal neurons; synapsin I is phosphorylated by residual Ca^{2+} acting through CaMKII to untether vesicles from actin and increase both the RRP and the probability of vesicle release from that pool (Cesca et al., 2010; Valente et al., 2012). Other proteins implicated in facilitation and/or potentiation include neuronal Ca^{2+} sensor-1 in mice (Sippy et al., 2003) and scribble in *Drosophila* (Roche et al., 2002).
9. Calmodulin-dependent binding of Ca^{2+} to munc13 isoforms that interact with RIM1 mediates the augmentation phase of release enhancement in mouse hippocampal synapses (Junge et al., 2004), while PTP at rat calyx of Held arises from Ca^{2+}

activation of protein kinase C to increase release probability (Korogod et al., 2007) and of myosin light chain kinase to increase the RRP capacity (Lee et al., 2008).

10. One mechanism by which Ca^{2+} can facilitate release is by binding to highly saturable endogenous buffers like calbindin-D28k, reducing their capability of rapidly capturing Ca^{2+} entering in successive action potentials. Buffer saturation is the dominant mechanism for facilitation at some (Blatow et al., 2003), but not other (Rozov et al., 2001) vertebrate central synapses.
11. Another factor that contributes to facilitation at some synapses is a facilitation of presynaptic Ca^{2+} currents that occurs in response to repeated action potentials (Xu et al., 2007).
12. Finally, residual Ca^{2+} can induce vesicle−vesicle fusion, resulting in exocytosis of compound vesicles and consequent increase in the average quantal size, contributing to PTP (He et al., 2009; Xue and Wu, 2010).

The multifarious processes that can lead to a short-term enhancement of transmitter release often occur in combination, especially at synapses displaying strong facilitation (Pan and Zucker, 2009). Facilitation's duration is governed mainly by the decay of $[Ca^{2+}]$ at its site(s) of action at docked vesicles, whereas that of augmentation is set by the time course for removal of residual Ca^{2+} from entire boutons after a moderate tetanus. Potentiation lasts longer after a strong tetanus because of overloading of processes responsible for removing Ca^{2+} from neurons. These processes include Ca^{2+} extrusion pumps, such as the plasma membrane ATPase and Na^+−Ca^{2+} exchange, and Ca^{2+} uptake into organelles such as endoplasmic reticulum and mitochondria (Fossier et al., 1992; Tang and Zucker, 1997; David et al., 1998). The accumulation of Ca^{2+} in mitochondria during a tetanus and its gradual posttetanic release into cytoplasm produce a prolonged elevation in residual $[Ca^{2+}]_i$ to generate PTP (Tang and Zucker, 1997; Lee et al., 2008). In addition, Na^+ accumulation during tetanic activity prolongs residual Ca^{2+} by reducing its extrusion by Na^+−Ca^{2+} exchange (Zhong et al., 2001).

Short-Term Heterosynaptic Depression and Facilitation

In short-term heterosynaptic plasticity, the strength of the synapse between two neurons is regulated by a third neuron or pathway extrinsic to the synapse under investigation. Although the conditions that give rise to this form of plasticity differ from those of short-term homosynaptic plasticity, modulation of some of the same effector molecules or pathways may be involved. Common targets include voltage-gated ion channels and Ca^{2+} signaling.

Short-term Heterosynaptic Depression

A classic example of presynaptic inhibition is found within the spinal cord, wherein a conditioning volley in a primary afferent results in a subsequent decrease in synaptic transmission between the presynaptic afferent and its postsynaptic motor neuron and at neighboring synapses of similar function. Depression of the motor neuron EPSP can persist for up to a few hundred milliseconds and perhaps even as long as seconds (Frank and Fuortes, 1957; Eccles et al., 1962; Willis, 2006). Interestingly, this form of inhibition is sensitive to drugs that interfere with the actions of the neurotransmitter GABA, yet neither the afferent nor motor neuron is GABAergic. This finding suggests that the strength of the afferent-motor neuron synapse is regulated by a third neuron or pathway. Descending projections from the brain can similarly inhibit the motor neuron EPSP (Castro et al., 2007; Yuan et al., 2009; Rudomin and Schmidt, 1999). A mechanism that contributes to both examples of depression is the release of GABA from interneurons that are activated by the conditioning volley in the afferent or descending pathways, respectively. The released GABA not only activates presynaptic $GABA_A$ receptors on an afferent terminal to open $GABA_A$-mediated Cl^- conductances that shunt the action potential, it also depolarizes the afferent terminal due to its relatively depolarized Cl^- reversal potential. This depolarization drives Na^+ channel inactivation (Chapters 12−14). The action potential is thus negatively affected, leading to a decrease in presynaptic Ca^{2+} entry through voltage-gated channels and a reduction in neurotransmitter release at the afferent-motor neuron synapse. A similar GABAergic mechanism of presynaptic inhibition occurs at the crayfish neuromuscular junction (Dudel and Kuffler, 1961), posterior pituitary nerve terminals (Zhang and Jackson, 1993) and at hippocampal mossy fiber synapses (Ruiz et al., 2003; Alle and Geiger, 2007; Ruiz and Kullmann, 2012). In addition to activating $GABA_A$ receptors, released GABA may also activate G-protein coupled $GABA_B$ receptors on afferent terminals (Barber et al., 1978; Price et al., 1984; Alford and Grillner, 1991; Towers et al., 2000). Activation of presynaptic $GABA_B$ receptors can lead to a relatively slow and prolonged G-protein-mediated inhibition of presynaptic voltage-gated Ca^{2+}-channels (Dolphin, 2003; Zamponi and Currie, 2013; see also Chapters 10 and 13) and thus, a decrease in the release of neurotransmitter evoked by subsequent action potentials.

In *Aplysia*, activation of neurons containing the tetrapeptide Phe-Met-Arg-Phe-NH_2 (FMRFa) produces presynaptic inhibition of the connections between sensory

neurons and motor neurons (Mackey et al., 1987; Small et al., 1992). FMRFa induces both short- and long-term (see later section) synaptic depression. Short-term depression, which has been observed in both cultures and ganglia (Pieroni and Byrne, 1992; Guan et al., 2003), emerges at least in part from activation of G-protein coupled FMRF receptors that modulate ionic conductances, thereby altering presynaptic Ca^{2+} entry, and by modulation of the machinery that regulates transmitter release (Belardetti et al., 1987; Piomelli et al., 1987; Dale and Kandel, 1990; Critz et al., 1991).

Within the mammalian brain, neuroactive substances that mediate short-term heterosynaptic depression often act in a diffuse manner. For example, GABA released from interneurons in the hippocampus and cerebellar cortex can activate $GABA_B$ receptors located on neighboring excitatory presynaptic terminals to decrease stimulus-evoked presynaptic Ca^{2+} entry and thus, neurotransmitter release (Isaacson et al., 1993; Dittman and Regehr, 1997; Vogt and Nicoll, 1999; Mitchell and Silver, 2000a). Similarly, both excitatory (Scanziani et al., 1997; Vogt and Nicoll, 1999; Von Gersdorff et al., 1997) and inhibitory (Mitchell and Silver, 2000b) synaptic transmission can be inhibited via G-protein-coupled receptors activated by the spillover of glutamate released at one synapse onto neighboring synapses. Again, a reduction in the stimulus-evoked rise in presynaptic Ca^{2+} has been implicated (Faas et al., 2002). Monoamine neurotransmitters and neuropeptides may also act diffusely to give rise to short-term heterosynaptic depression.

Short-term Heterosynaptic Facilitation

The most extensively studied example of heterosynaptic facilitation is the serotonin-induced facilitation of the *Aplysia* sensorimotor synapse, which has both short-lasting (minutes) and long-lasting (days) forms. Short-term (minutes) heterosynaptic facilitation is induced when a single, brief train of shocks is delivered to the body wall of the animal. This process results in the release of modulatory transmitters, such as serotonin (5-HT), from a distinct class of interneurons (IN) referred to as facilitatory neurons (Fig. 18.4A1). These facilitatory neurons regulate the properties of the sensory neurons (SN) and the strength of their connections with postsynaptic interneurons and motor neurons (MN) through a process called *heterosynaptic facilitation* (Byrne and Kandel, 1996; Figs. 18.4A2 and 18.4A3). The molecular mechanisms contributing to short-term heterosynaptic facilitation are illustrated in Fig. 18.4B. Serotonin binds to multiple types of G-protein-coupled receptors localized in the membrane of SNs and activation of these receptors recruits at least two predominant signaling cascades in the SNs: the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) and the diacylglycerol/protein kinase C (DAG/PKC) cascades (Byrne and Kandel, 1996). Ca^{2+}/calmodulin-dependent protein kinase (CaM kinase II) appears to be

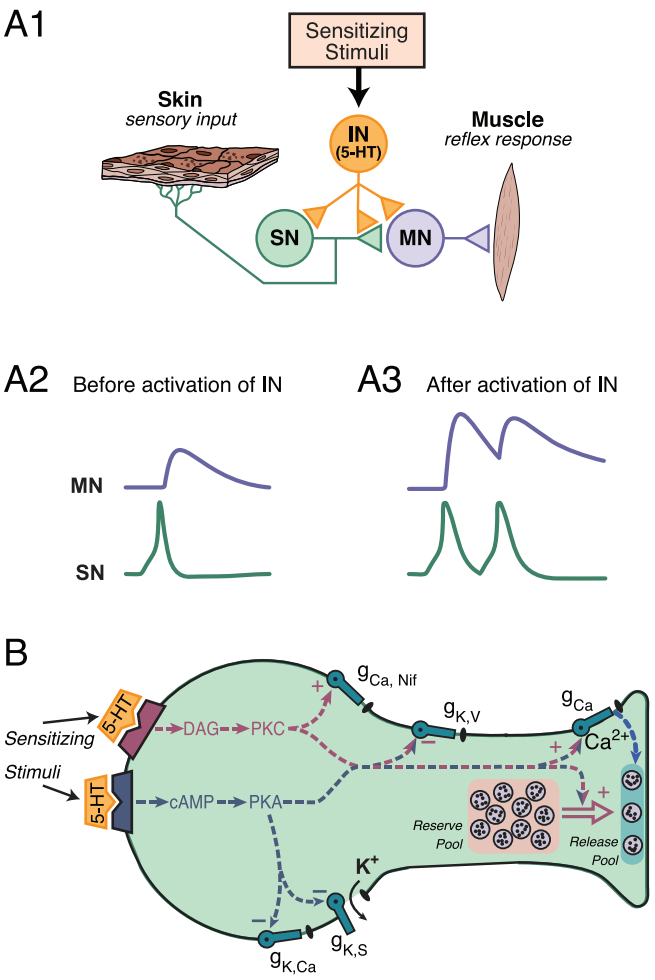

FIGURE 18.4 Model of short-term heterosynaptic facilitation of the sensorimotor connection that contributes to short-term sensitization in *Aplysia*. (A1) Sensitizing stimuli activate facilitatory interneurons (IN) that release modulatory transmitters, one of which is 5-HT. The modulator leads to an alteration of the properties of the sensory neuron (SN). (A2 and A3) The enhanced synaptic input to the motor neuron (MN) (A3) results from enhanced sensory input, partly due to two mechanisms. First, the same peripheral stimulus can evoke a greater number of action potentials in the presynaptic SN (i.e., enhanced excitability). Second, each action potential fired by an SN produces a greater synaptic response in the MN (i.e., synaptic facilitation). (B) Model of a SN that depicts the multiple processes for short-term facilitation and changes in excitability that contribute to short-term sensitization. 5-HT released from facilitatory neurons binds to at least two distinct classes of receptors on the outer surface of the membrane and leads to the transient activation of two intracellular second messengers, DAG and cAMP, and their respective kinases (PKC and PKA). These kinases affect multiple cellular processes, the combined effects of which lead to changes in excitability and enhanced transmitter release when subsequent action potentials are fired in the sensory neuron (see text for additional details). *Modified from Byrne and Kandel (1996).*

engaged as well. PKA and PKC have multiple targets, including membrane ion channels, thus affecting the spike waveform and the excitability of the SN. For example, activation of the PKA and PKC cascades modifies various Ca^{2+} and K^+ channels, leading to an enhanced spike activity (i.e., enhanced excitability), and broadening of the action potential. Reflections of enhanced excitability include an increase in the number of action potentials elicited in a sensory neuron by a fixed extrinsic current injected into the cell or by a fixed stimulus to the skin (Fig. 18.4A3). Spike broadening leads to enhanced Ca^{2+} influx in presynaptic terminals and facilitates transmitter release.

In addition to spike broadening, spike-duration-independent mechanisms of enhanced transmitter release have been implicated in 5-HT-induced heterosynaptic facilitation. These mechanisms involve direct modulation of a presynaptic Ca^{2+} conductance independently of spike broadening (Leal and Klein, 2009) as well as an increase in the number of transmitter-containing synaptic vesicles that become available for release, possibly through synapsin-regulated vesicle mobilization (Byrne and Kandel, 1996; Angers et al., 2002; Zhao and Klein, 2002; Fioravante et al., 2007). This process is represented in Fig. 18.4B (large open arrow) as the translocation or mobilization of transmitter vesicles from a reserve pool to a releasable pool, resulting in an increase in the number of transmitter-containing vesicles available for release with subsequent action potentials in the sensory neuron. The maintenance of short-term facilitation is dependent on the persistence of the PKA- and PKC-induced phosphorylation of the various substrate proteins. Prolonged treatment with 5-HT (1.5 h) also activates mitogen-activated protein kinase (MAPK) (for review see Sharma and Carew, 2004). However, this pathway appears to be important only for the induction of longer-term processes (see section on long-term heterosynaptic facilitation).

The consequences of activating these multiple second-messenger systems and modulating these various cellular processes are expressed when test stimuli elicit action potentials in the sensory neuron at various times after the presentation of the sensitizing stimuli (Fig. 18.4A3). More transmitter is available for release as a result of the mobilization process and each action potential results in a larger influx of Ca^{2+} to trigger release of the available transmitter. This facilitation of transmitter release from the sensory neuron leads to a larger postsynaptic potential in the motor neuron.

Of general significance is the observation that a single modulatory transmitter (i.e., 5-HT) activates multiple kinase systems. The involvement of multiple second messenger systems in synaptic plasticity also appears to be a theme emerging from mammalian studies. For example, the induction of LTP in the CA1 area of the hippocampus appears to involve MAPK, PKC, CaM kinase II, and tyrosine kinase (reviewed in Dineley et al., 2001; Miyamoto, 2006).

Summary I

Synapses may show a decline in transmission (depression) or an increase in synaptic efficacy as a function of prior activity, with time constants ranging from seconds (facilitation and augmentation) to minutes (potentiation or PTP) to hours (LTP—see next section); many synapses show a mixture of several of these phases. Depression makes synapses selectively responsive to brief stimuli or to changes in level of activity, contributes to simple forms of learning such as habituation, alters synaptic dynamic range, and can reduce noise, tune receptive fields, and regulate oscillatory behavior in networks (Abbott et al., 1997; Abbott and Regehr, 2004; Antzoulatos and Byrne, 2004; Mamiya and Nadim, 2005; David et al., 2009; Khanbabaie et al., 2010; Patel et al., 2012; Vickers et al., 2012). Short-term, homosynaptic depression may be due to depletion of a readily releasable pool of vesicles, the inhibitory action of transmitter on presynaptic autoreceptors, Ca^{2+} channel inactivation, or release site inactivation or refractoriness. Short-term heterosynaptic depression may be due to modulation of ionic conductances, Ca^{2+} entry, and changes in the release machinery.

Frequency-dependent increases in synaptic efficacy are due to the effects of residual presynaptic Ca^{2+} acting to modulate the release process. At least part of Ca^{2+} action is mediated by separate targets for facilitation and for augmentation and potentiation. At some synapses, endogenous buffer saturation also plays a role. PTP is prolonged after a long tetanus because overloaded Ca^{2+} removal processes leave presynaptic $[Ca^{2+}]_i$ elevated for minutes after such activity. These frequency-dependent increases in synaptic efficacy constitute a high-pass filtering that allows synapses to distinguish significant signals from noise, respond to selected patterns of activity, and optimize synaptic information transmission (Abbott and Regehr, 2004; Pfister et al., 2010; Rotman et al., 2011). Short-term heterosynaptic facilitation, like short-term heterosynaptic depression, is due to modulation of ionic conductances, Ca^{2+} entry, and changes in the release machinery, although the effects are such that EPSPs are facilitated rather than depressed. A common site of both homosynaptic and heterosynaptic forms of plasticity is regulation of some aspect of Ca^{2+} influx or Ca^{2+}-dependent processes. This common theme is not surprising given the central role that Ca^{2+} plays in transmitter release.

LONG-TERM PLASTICITY

Long-term synaptic plasticity refers to changes in synaptic efficacy that persist for at least several hours, and possibly for the lifetime of the organism. Such long-lasting changes are then candidates for the substrates of long-lasting memories. Long-term synaptic plasticity, like short-term plasticity, is bidirectional. In mammalian systems a long-lasting increase in synaptic efficacy is typically called *long-term potentiation* (LTP) and a decrease in efficacy is called *long-term depression* (LTD). In invertebrates, the term *long-term facilitation* (LTF) is often used to describe the increase in efficacy.

Long-Term Plasticity as a Mechanism for Learning and Memory and for Shaping the Responses of Sensory Cells to Sensory Stimuli

The idea that associations and temporal contiguity can be used as a basis for learning has been around at least since the era of the Greek philosophers. In order to take the next step and postulate what mechanisms can implement such correlational learning, some knowledge of the brain is necessary. Already in the late 19th century, with the advent of anatomical techniques, Ramón y Cajal postulated that such learning could be implemented via the reinforcement of existing pathways between neurons and the formation of new pathways. This idea was elucidated by Donald Hebb in 1949 (Hebb, 1949) who famously said:

> When an axon in cell *A* is near enough to excite cell *B* and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that *A*'s efficacy in firing *B* is increased.

Such correlational forms of plasticity are now often called Hebbian plasticity. A prominent form of LTP is Hebbian in that it requires activity of both the presynaptic and postsynaptic cells. Various theoretical studies pointed out that Hebbian potentiation alone has several pitfalls: First, synapses have a limited dynamic range, and therefore, potentiation alone will eventually cause all synapses to saturate at their maximal level, making all neurons nonselective and identical in their response (Rochester et al., 1956; Stent, 1973). Second, Hebbian plasticity is sensitive to correlations between pre- and postsynaptic spiking, but spurious correlations between pre- and postsynaptic firing are generally observed and such correlations would cause LTP when it is undesirable; appropriately designed Hebbian rules should remove these spurious correlations, whereas Hebbian LTP alone cannot (Sejnowski, 1977). In addition, various experimental results cannot be explained by LTP alone (Cooper et al., 1979; Bienenstock et al., 1982). However, many of these limitations of Hebbian plasticity can be resolved if synapses also exhibit activity-dependent reduction in synaptic efficacy. Long lasting, activity-dependent reduction in synaptic efficacies, usually referred to as LTD, has since been demonstrated experimentally. Therefore, long-term synaptic plasticity is a bidirectional process (Malenka and Bear, 2004).

Long-term synaptic plasticity was proposed as the basis for learning and memory before the actual experimental discovery of synaptic plasticity. Over the years, experimental evidence has accumulated in support of this thesis (see Box 18.1 and Chapter 20). In addition to serving as the basis of learning and memory, long-term synaptic plasticity also shapes the responses of sensory cells to sensory stimuli. In sensory modalities the concept of a receptive field is often used to characterize the response properties of cortical cells. The term *receptive field* was originally characterized for sensory cells, and corresponded to the area of the skin which when stimulated elicits a response from that cell (Sherrington, 1906). The concept was later generalized to other sensory modalities. In the visual system, it characterizes not only the spatial location of stimuli that elicit a visual response, but also the properties of such stimuli—for example, the preferred orientation. In the auditory system, it is usually characterized by the frequency bands that elicit a cellular response. Many properties of receptive fields can change by altering the sensory environment; such modifications are called receptive field plasticity. Receptive field plasticity is prominent especially in the first weeks, months or years of life (depending on the animal or the modality), but some forms of it can be found throughout life.

The contribution of long-term synaptic plasticity to the formation of cortical receptive fields has been documented extensively in visual cortex, where it has been shown to be crucial for ocular dominance plasticity (Kleinschmidt et al., 1987; Roberts et al., 1998) and for the formation of orientation selectivity (Ramoa et al., 2001). Similar effects have been documented in somatosensory (Glazewski et al., 1996) and auditory cortex (Weinberger et al., 1993). Receptive field plasticity can also be considered a form of learning, usually referred to as unsupervised learning in the literature on machine learning.

Homosynaptic Bidirectional Plasticity

Homosynaptic LTP was first demonstrated by Bliss and Lomo in 1973 (Bliss and Lomo, 1973; Bliss and Collingridge, 1993). They stimulated the hippocampal perforant path and recorded the resulting long-term

BOX 18.1

IS SYNAPTIC PLASTICITY THE MECHANISTIC BASIS OF LEARNING AND MEMORY?

Synaptic plasticity is typically characterized in a reduced preparation such as a brain slice. How is it possible to determine whether a phenomenon observed in a brain slice is indeed responsible for learning and memory in an intact animal? A set of four criteria have been proposed by Martin and Morris (Martin et al., 2000; Martin and Morris, 2002). These criteria are:

1. Detectability. If learning is based on synaptic plasticity, then when learning occurs, synapses must be modified, and such changes should be experimentally detected.
2. Mimicry. A new memory or learning can be installed directly by appropriately changing a set of synapses in the brain.
3. Anterograde Alteration. An intervention known to prevent synaptic plasticity would also prevent new learning and memory formation.
4. Retrograde Alteration. An intervention that alters synaptic efficacies after a memory or new learning has been established should also alter or erase the animal's memory of that event.

Although mimicry is beyond the reach of current techniques, there has been significant progress in implementing the other criteria. Anterograde alteration is a common procedure as various pharmacological agents and genetic manipulations that are known to prevent LTP have also been shown to prevent certain forms of learning (Davis et al., 1992; Giese et al., 1998). Detectability is more difficult to establish, but there have been several experiments showing changes in synaptic efficacy during new learning (Rioult-Pedotti et al., 2000; Whitlock et al., 2006). Retrograde alteration has primarily been demonstrated using pharmacological techniques that reverse the late phase of LTP by blocking the activity of atypical isoforms of PKC (Pastalkova et al., 2006). Such techniques can also erase memories long after they have been established (Pastalkova et al., 2006; Shema et al., 2007). The contributions of synaptic plasticity to learning and memory are discussed in more detail in Chapter 20.

enhancement of synaptic transmission in dentate gyrus (DG in Fig. 18.5A). However, since then, the canonical preparation for studying LTP has been the hippocampal slice, and specifically, the plasticity induced at CA1 synapses (Fig. 18.5A). In these experiments, a recording electrode is placed intracellularly in the soma of a CA1 neuron or an extracellular electrode is placed in the synaptic layer of these neurons. In the case of intracellular recordings, either EPSPs or the excitatory postsynaptic current (EPSCs) are recorded (see Chapter 16). The extracellular recordings detect field EPSPs (fEPSP), which are a summation of synaptic events in the vicinity of the recording electrode. Ideally, the responses to stimulation in two independent pathways are recorded for at least 15 min; these responses are called baseline recordings. Baseline recordings from the two pathways are typically carried out at a low frequency (1–2 per min) and to a moderate stimulus intensity, and recording conditions are considered adequate only if the baseline is relatively stable and shows no systematic drift. Subsequently, a conditioning stimulus is delivered to one of the pathways (the conditioning pathway, blue in Fig. 18.5B), while the control pathway (red) is unstimulated. Many different conditioning protocols have been used, but a typical conditioning stimulus is a high-frequency stimulus (HFS) in the range of 50–200 Hz for a few seconds. After the conditioning stimulus is delivered, baseline recording is resumed. In an LTP protocol, the magnitude of the synaptic potential is increased after the conditioning stimuli. If there is no change in the control pathway then the plasticity that is observed is considered homosynaptic LTP.

An observation of LTP at the conditioned pathway but not the control pathway is called synapse specificity, a term which, to a large extent, overlaps with the term homosynaptic plasticity. However, an experiment like the one described above does not sufficiently describe the spatial resolution of the specificity because, in such experiments, these pathways typically lie on different dendritic branches, and therefore these experiments cannot discern whether two nearby synapses are controlled separately by LTP induction protocols. More recent techniques (Matsuzaki et al., 2004; Bagal et al., 2005; Harvey and Svoboda, 2007) allow stimulation of single synapses by optically uncaging neurotransmitter near a single synaptic spine. The results of such experiments indicate that LTP can be very spatially restricted,

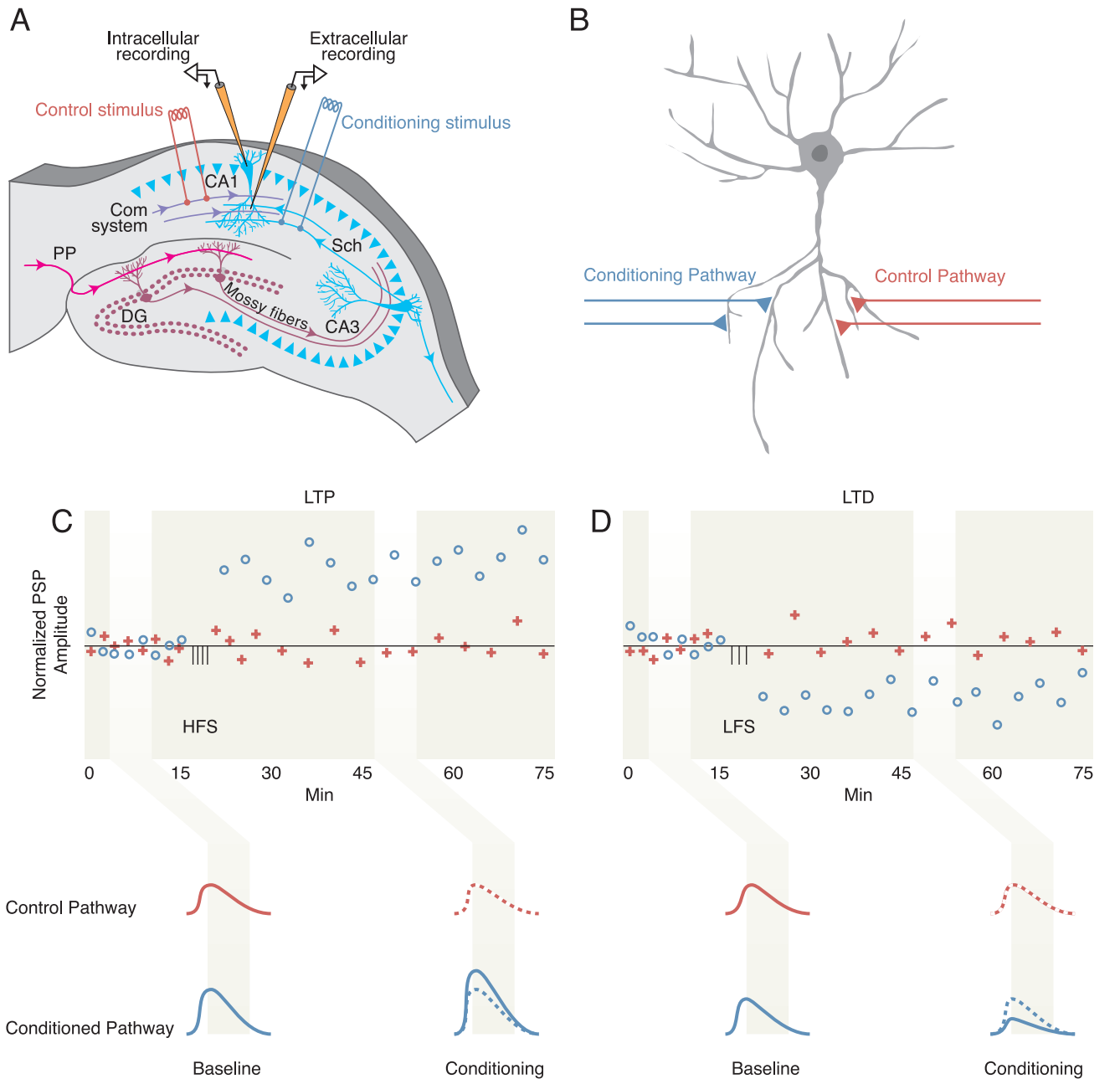

FIGURE 18.5 **Induction of bidirectional synaptic plasticity.** (A) The hippocampus is the canonical preparation for analyses of synaptic plasticity in the CNS. Typically, intracellular or extracellular recordings are carried out in CA1, and the stimuli are delivered to the axons in the Schaffer collateral (Sch). However, other parts of the hippocampus, such as CA3 or the dentate gyrus (DG), are also sometimes used. (B) A schematic diagram of a CA1 neuron with two nonoverlapping conditioning and control pathways. (C) An example of an LTP induction protocol using high-frequency stimulation (HFS). Before the stimulation, a baseline is recorded in both the conditioning and control pathways. During conditioning, a HFS is delivered only to the conditioning pathway, and LTP is observed only in the conditioned and not in the control pathway. Below: postsynaptic potentials (PSPs) before and after HFS are displayed and contrasted with the potentials during baseline (dashed lines). (D) LTD is induced using a low-frequency stimulus (LFS). This procedure induced homosynaptic LTD, because the PSPs in the control pathways do not change.

although in some cases plasticity in one synapse can affect subsequent plasticity at nearby synapses (Harvey and Svoboda, 2007).

Homosynaptic LTP occurs when the presynaptic and postsynaptic neurons are active in close temporal proximity; it is therefore similar to the original idea proposed by Hebb (Hebb, 1949). As described above, various theoretical studies indicated that LTP alone is insufficient to account for experimental observations and that LTD is necessary as well (Rochester et al., 1956;

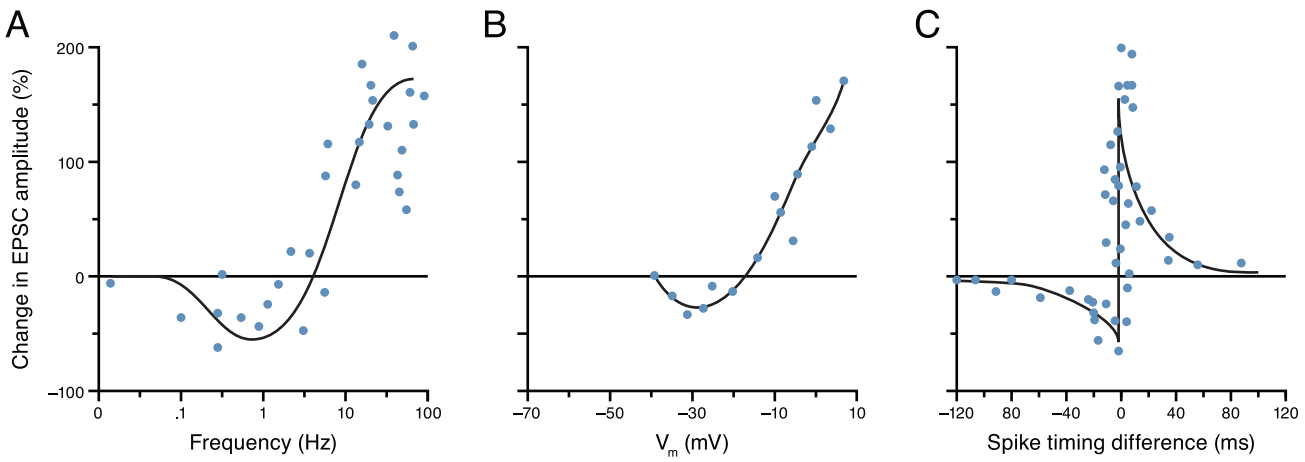

FIGURE 18.6 **Various induction protocols of bidirectional synaptic plasticity.** (A) Rate-based induction. In this protocol the presynaptic afferents are stimulated at different frequencies. If they are stimulated with a low frequency, as in Fig. 18.5D, LTD is induced. If they are stimulated with a high frequency as in Fig. 18.5C, LTP is induced. (B) Pairing induced plasticity. A low frequency presynaptic stimulation is applied and at the same time the postsynaptic cell is patch clamped and held at a set voltage. If the postsynaptic cell is weakly depolarized, LTD is induced. If it is strongly depolarized, LTP is induced. (C) Spike timing dependent plasticity (STDP). Here, intracellular recordings are made from the postsynaptic cell, and the presynaptic afferents are stimulated either extracellularly or intracellularly. Both presynaptic afferents and the postsynaptic cell are caused to fire repeatedly at a low frequency, with a small timing difference. If the spike timing difference is positive, then the presynaptic cell fired before the postsynaptic cell. When it is negative, the order is reversed. For positive spike timing LTP is typically induced and for negative spike timing LTD is induced. However, many other parameters such as the stimulation frequency also control the sign and magnitude of synaptic plasticity.

Stent, 1973; Sejnowski, 1977; Cooper et al., 1979; Bienenstock et al., 1982). Following these theoretical ideas, experimentalists set out in search of LTD. In 1992, two groups observed homosynaptic LTD in the hippocampus (Dudek and Bear, 1992; Mulkey and Malenka, 1992; Malenka and Bear, 2004). LTD was induced by a low-frequency stimulus (LFS) in the range of 0.5−10 Hz, and typically, many repetitions (~900) were used to induce a significant level of LTD (Fig. 18.5D). Induction protocols in which the sign and magnitude of synaptic plasticity are controlled by the rate of presynaptic stimulation, such as HFS and LFS, are often referred to as rate-based protocols.

Although the canonical preparation for studying long-term synaptic plasticity is the hippocampal slice, LTP can be induced in a very wide array of brain systems ranging from the spinal cord (Ji et al., 2003) to the neocortex of mammals (Bear and Kirkwood, 1993) and nonmammalian systems and invertebrates (Baxter et al., 1985; Zhang et al., 1998; Cassenaer and Laurent, 2007), including *Aplysia* (Walters and Byrne, 1985; Roberts and Glanzman, 2003). In the cerebellum, where synaptic plasticity and its functional consequences are also well studied, the canonical form of plasticity is LTD of parallel fiber synapses onto Purkinje cells (see Chapters 19 and 20) rather than LTP (Ito, 1989). This form of LTD was discovered before hippocampal LTD, but because it is observed at the input connections to a neuron whose output is inhibitory, LTD functionally results in disinhibition, and is therefore in some sense similar to LTP in that it leads to enhanced excitation of downstream neurons. Cerebellar LTD induction depends on co-activation of two pathways, the parallel fiber and climbing fiber pathways. Therefore, this LTD is also similar to hippocampal LTP in that it depends on positive correlations and coincidences of its inputs. In the cerebellum, LTP has been observed as well (Lev-Ram et al., 2002), which reinforces the general observation and theoretical suggestion that plasticity is, in general, bidirectional.

Induction Protocols

The induction of bidirectional synaptic plasticity by stimulation of afferent fibers at various rates (Fig 18.5C, D and Fig. 18.6A) and its measurement using extracellular recording techniques are very common because this approach is relatively simple from a technical perspective. However, such rate-based protocols do not allow for independent control of the postsynaptic cell. Rather, activation of the postsynaptic neuron depends upon the activation of the presynaptic afferents. By contrast, by recording intracellularly from the postsynaptic cell, the postsynaptic cell can be presented with a stimulation protocol that is controlled by the experimenter. One example of the latter is a pairing protocol in which low frequency presynaptic stimulation is maintained and paired with depolarization of the postsynaptic cell. LTP is induced if the postsynaptic cell is depolarized sufficiently (Fig. 18.6B). Interestingly, if the cell is only moderately depolarized, LTD is induced (Fig. 18.6B). Such pairing protocols

have been used in many brain areas and systems including the hippocampus (Ngezahayo et al., 2000) and neocortex (Artola et al., 1990).

Spike timing dependent plasticity (STDP) is another frequently used induction protocol. This protocol is believed to better resemble naturally occurring spike patterns (Markram et al., 1997; Ngezahayo et al., 2000; Feldman, 2000; Sjöström et al., 2001). In STDP, the pre- and postsynaptic cells are repeatedly fired with a fixed delay between the pre- and postsynaptic firing times. When the presynaptic cell is fired within a window of ~0–30 ms before the postsynaptic cell, LTP is often observed (Fig. 18.6C). However, the induction of spike timing dependent LTP also depends on other parameters, such as the firing frequency, and it sometimes requires more than a single postsynaptic spike (reviewed in Shouval et al., 2010). Interestingly, if the postsynaptic spike arrives tens of milliseconds before the presynaptic spike, LTD is induced (Fig. 18.6C). Under some experimental conditions LTD is also induced when the presynaptic spike arrives ~30–60 ms before the postsynaptic action potential (Nishiyama et al., 2000; Wittenberg and Wang, 2006). STDP is often described as a more physiological induction protocol. However, STDP requires the precise and regularly repeated sequence (50–100 times) of post- and presynaptic stimuli, which may not necessarily resemble naturally occurring activity patterns.

STDP experiments demonstrate unequivocally that the timing interval between pre- and postsynaptic spikes affects synaptic plasticity; however, intervals between spike pairs are not the sole determinant of the sign and magnitude of synaptic plasticity. Various experiments have shown that, apart from spike pair intervals, the frequency at which the pairs are delivered affects synaptic plasticity (Markram et al., 1997; Sjöström et al., 2001; Wittenberg and Wang, 2006), that more complex spike patterns cannot simply be accounted for by plasticity evoked by spike pairs (Froemke and Dan, 2002; Wittenberg and Wang, 2006), and even the number of pairs delivered can change the direction of the plasticity that is induced (Wittenberg & Wang, 2006). In general, plasticity evoked by arbitrary spike patterns cannot be accounted for simply by knowing the temporal intervals between all spike pairs (Shouval et al., 2010).

Another induction protocol, designed specifically to mimic conditions in the hippocampus, is the theta burst protocol (Staubli and Lynch, 1987). Unlike STDP or pairing induced plasticity, this protocol can be induced extracellularly, without the need for intracellular electrodes. In theta burst induction, a burst of high-frequency presynaptic stimuli is repeatedly delivered at a frequency between 5–10 Hz; the same frequency range as the naturally occurring theta rhythm in hippocampus. In some cases (Huerta and Lisman, 1995), a seemingly natural theta frequency can be replicated in slices by cholinergic stimulation. In such a preparation, if the presynaptic bursts are given near the peak of the oscillation, LTP is established, but the same protocol delivered near the trough results in LTD.

Although a diverse set of possible induction protocols exist for synaptic plasticity, most of these protocols cause the induction of synaptic plasticity through mechanisms that share common components. Once these common mechanisms are understood, it is possible to more easily understand what forms of plasticity are induced by the different induction protocols. Induction protocols for synaptic plasticity control the activity of the pre- and postsynaptic neurons. In all commonly used paradigms, spiking is directly induced in the presynaptic afferents. The postsynaptic neuron can either be forced to spike directly, as in STDP protocols, to spike indirectly through the stimulation of its presynaptic afferents as in rate-based protocols, or is simply depolarized, as in pairing protocols. For a synapse to change its efficacy differentially in response to a particular stimulation condition, a synapse must have a mechanism that is sensitive to the pre- and postsynaptic activity patterns. Furthermore, this mechanism must signal to the synapse the nature of the change in synaptic efficacy indicated by the pre- and postsynaptic spike sequences. This process is referred to as induction. The actual change, which determines the synaptic efficacy, is called the expression mechanism. We first discuss induction.

Induction and the Role of NMDA Receptors in Long-Term, Hebbian LTD and LTP

The most prominent common component of induction in many forms of LTP is the activation of NMDA receptors (Bliss and Collingridge, 1993). NMDA receptors (NMDARs) are excitatory glutamate receptors (see Chapters 10 and 16) that possess several features well-suited for the induction of LTP, and specifically, for the Hebbian nature of LTP. The NMDAR dependence of LTP is easily demonstrated by using selective NMDAR antagonists, which eliminate LTP.

Most excitatory synaptic current in the brain is conveyed by the AMPA subtype of glutamate receptors (Fig 18.7A, see Chapters 10 and 16). AMPA receptors are activated via the binding of glutamate, and although some AMPA receptors are permeable to Ca^{2+}, this permeability is relatively low. In contrast, NMDARs have a high Ca^{2+} permeability relative to AMPA receptors and slower kinetics. Importantly, NMDARs located on the postsynaptic neuron primarily convey current when the postsynaptic cell is depolarized. Mechanistically, the voltage-dependence of the NMDAR mediated current is caused by the ability of

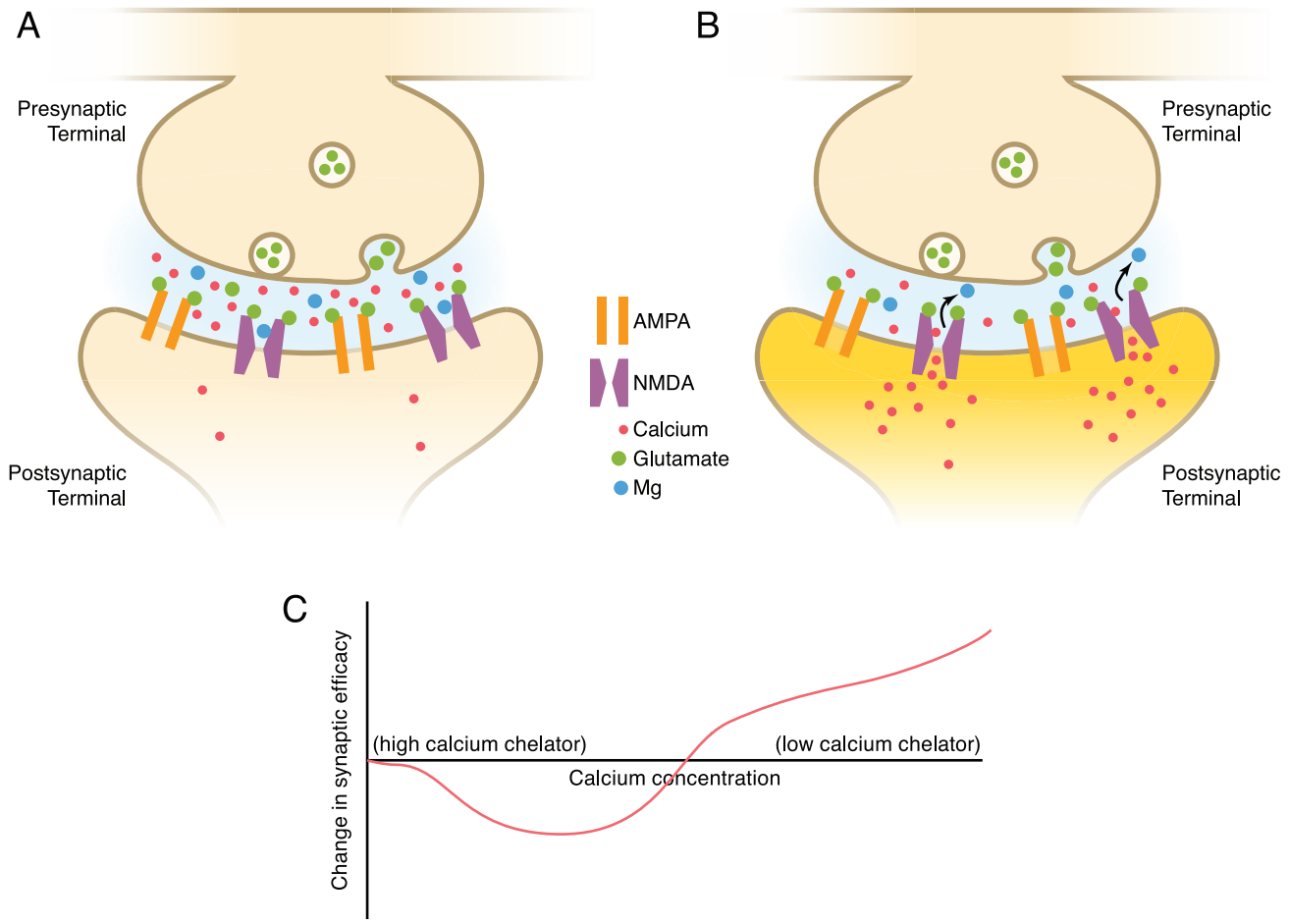

FIGURE 18.7 **Mechanisms of induction.** (A) The postsynaptic portion of the excitatory synapse typically has the shape of a spine. It includes various types of glutamate receptors. Most synaptic current is typically conveyed by AMPA receptors that are opened when they bind glutamate that is released from the presynaptic cell. AMPA receptors are permeable primarily to Na^+ and K^+. The spine also has NMDA receptors that bind glutamate. NMDA receptors are voltage dependent, and at resting membrane potentials, they are blocked by Mg^{2+} (blue circles). (B) During the induction of LTP, glutamate that is released from the presynaptic cell binds to glutamate receptors on the postsynaptic cell, the postsynaptic cell is depolarized (indicated by the change in color of the spine), and the Mg^{2+} block of the NMDA receptor is relieved. Ca^{2+} entering through NMDA receptors or voltage-dependent channels then triggers a biochemical cascade that results in synaptic plasticity. (C) Synaptic plasticity is bidirectional. Moderate levels of postsynaptic Ca^{2+} cause the induction of LTD whereas high levels result in LTP.

extracellular Mg^{2+} to block the pore of the NMDAR when the neuron is at rest (Chapters 10 and 16). However, when the postsynaptic cell is depolarized, for example by a postsynaptic action potential, the Mg^{2+} block is removed (Fig 18.7B). The voltage-dependence of the NMDAR conductance allows NMDARs to function as coincidence detectors; they conduct a significant amount of current only when both the presynaptic afferent and postsynaptic cell are co-active. This coincidence detection property of the NMDA receptor is what makes long-term synaptic plasticity Hebbian.

Because NMDARs are Ca^{2+} permeable, the postsynaptic concentration of Ca^{2+} is an indicator of their activity, and hence a reporter of coincident pre- and postsynaptic activity. In synapses, as in many other biological systems, Ca^{2+} is a potent second messenger. During the induction of synaptic plasticity, Ca^{2+} is the primary signal that initiates the biochemical cascades that eventually result in the induction of LTP. If postsynaptic Ca^{2+} concentrations are reduced via the use of postsynaptic Ca^{2+} chelators (Cummings et al., 1996), LTP can be eliminated (Fig. 18.7C). Interestingly, Ca^{2+} also seems to be an important second messenger in some NMDAR-independent forms of synaptic plasticity (Galván et al., 2008).

Like LTP, LTD in many cases is also NMDAR dependent. It can be eliminated by NMDAR blockade and by chelation of postsynaptic Ca^{2+} (Cummings et al., 1996; Cho et al., 2001). It seems that LTD induction requires a moderate but prolonged activation of NMDARs, and a moderate postsynaptic Ca^{2+} influx, whereas LTP induction requires the strong activation of NMDARs and a large postsynaptic Ca^{2+} influx. The notion that a moderate level of Ca^{2+} produces LTD

stems from experiments in which a moderate inactivation of NMDARs or a moderate concentration of postsynaptic Ca^{2+} chelators converts the outcome of LTP induction protocols from LTP to LTD (Fig. 18.7C) (Cummings et al., 1996; Cho et al., 2001).

Zucker and colleagues (Yang et al., 1999) examined the relationship between postsynaptic Ca^{2+} levels and the sign of synaptic plasticity by directly controlling postsynaptic Ca^{2+} levels by the photolysis of caged-Ca^{2+}. A strong but brief uncaging stimulus, consistent with the generation of a large but brief Ca^{2+} transient, produced LTP, whereas a moderate, prolonged stimulus resulted in LTD. In contrast, truncating a large Ca^{2+} transient with the caged Ca^{2+} buffer diazo-2 showed that LTP induction only requires that Ca^{2+} be elevated for a few seconds (Malenka et al., 1992). Interestingly, in the cerebellum where LTP and LTD are also Ca^{2+}-dependent, high postsynaptic Ca^{2+} levels favor LTD and moderate Ca^{2+} levels favor LTP (Coesmans et al., 2004).

Bidirectional Plasticity and Postsynaptic Ca^{2+} in LTD and LTP

A strong, brief Ca^{2+} transient typically results in LTP, whereas a weaker, prolonged transient results in LTD in hippocampal neurons. But how are Ca^{2+} transients decoded and translated to the appropriate changes in synaptic efficacy? One prominent theory suggested that strong Ca^{2+} transients preferentially activate kinases, leading to LTP and that weaker transients gradually activate phosphatases leading to LTD (Lisman, 1989). Indeed, the activation of LTP depends upon kinases such as Ca^{2+}-calmodulin-dependent protein kinase II (CaMKII) (Malenka et al., 1989), whereas LTD depends upon phosphatases such as protein phosphatase 1 and protein phosphatase 2b (or calcineurin) (Mulkey and Malenka, 1992) (see Chapter 4 for review of kinases and phosphatases). The next section (Expression Mechanisms) reviews expression mechanisms of synaptic plasticity and explains the mechanisms by which kinases and phosphatases regulate synaptic efficacy.

The outcomes of the different induction protocols described here, together with the observations at the mechanistic level can be accounted for by a model based on a simple set of assumptions: 1) Ca^{2+} influx through NMDAR can account for many forms of synaptic plasticity; and 2) a moderate level of Ca^{2+} produces LTD, whereas a large concentration produces LTP (Lisman, 1989). These two assumptions alone can account for pairing induced plasticity, but they are not sufficient to account for other protocols, such as spike timing dependent LTD. However, spike timing dependent LTD as well as various other induction protocols can be accounted for with some additional assumptions about the properties of back-propagating action potentials in dendrites (see Chapter 17 and Shouval et al., 2002; Shouval et al., 2010).

Additional Mechanisms of LTP and LTD Induction

Although evidence for a role of NMDRs and Ca^{2+} elevation in the induction of LTP and LTD in CA1 neurons is rather strong, some studies argue for a more nuanced role for these players in bidirectional plasticity. In one study (Nabavi et al., 2013), induction of LTD in CA1 synapses was blocked by APV, a competitive inhibitor of the NMDA receptor, but not by MK801, which blocks the flow of ions through the NMDAR pore. In addition, this study found that whereas the addition of Ca^{2+} chelators modified the induction of LTP, they did not affect the induction of LTD. These results seem inconsistent with previous studies (Cummings et al., 1996; Cho et al., 2001) and with the direct induction of LTD via a moderate increase in concentration of postsynaptic Ca^{2+} (Yang et al., 1999). However, they raise the intriguing possibility of a metabotropic action of NMDAR on LTD induction that is triggered by the binding of glutamate to the NMDA receptor, rather than the flow of Ca^{2+} into the postsynaptic cell. In another study, the assumption that postsynaptic Ca^{2+} concentration determines the sign of synaptic plasticity was investigated by imaging Ca^{2+} levels in the dendritic spines of young neocortical neurons during the induction of STDP (Nevian and Sakmann, 2006). Although there was a correlation between the peak elevation of Ca^{2+} and the magnitude of plasticity, no clear correlation was found between the postsynaptic Ca^{2+} concentration and the sign of synaptic plasticity. Rather, the data suggested that LTP and LTD may be separate processes, each controlled by elevated postsynaptic Ca^{2+} acting at a different site.

NMDAR-independent LTP has also been reported. For example, LTP of the dentate gyrus afferents (mossy fibers) to CA3 cells of the hippocampus (Fig. 18.5A) is Ca^{2+} dependent, but NMDA-receptor independent (Nicoll and Malenka, 1995). In this form of LTP, Ca^{2+}enters the postsynaptic cell via activated voltage-gated Ca^{2+} channels rather than NMDARs (Kapur et al., 1998). Hence, such LTP might not be associative or Hebbian in nature. Even in the canonical CA1 preparation, LTP can depend on Ca^{2+} entry through postsynaptic voltage-gated Ca^{2+} channels either alone, or in combination with NMDARs (Morgan and Teyler, 1999). If LTP is induced by a 200-Hz stimulus rather than a 100-Hz stimulus, NMDAR independent LTP is induced, and this LTP depends on voltage-gated Ca^{2+} channels (Grover and Teyler, 1990). This result points to a simple conclusion: Ca^{2+} influx is essential for LTP, but under different conditions and in different preparations, the mechanism by which the Ca^{2+} rise occurs

may differ. Some Ca^{2+}-permeant channels such as NMDARs will be coincidence detectors, conveying a Hebbian property to LTP, whereas other Ca^{2+}-permeant channels will not.

Similarly, not all forms of LTD are NMDAR dependent. In the hippocampus, an mGluR-dependent LTD occurs in parallel to the NMDAR dependent LTD (Nicoll et al., 1998). In the neocortex, some LTD that depends on NMDAR might actually require the activation of *presynaptic*, rather than postsynaptic NMDAR (Sjöström et al., 2003), and such LTD might also require the activation of mGluRs as well as, in some cases, cannabinoid receptors (Sjöström et al., 2003; Bender et al., 2006). In neocortex, different cortical layers might exhibit different forms of LTD (Crozier et al., 2007).

Expression Mechanisms: Persistent Post- and Presynaptic Changes in Synaptic Transmission Mechanisms Underlying LTD and LTP

In the previous section we described the mechanisms that detect coincidences of pre- and postsynaptic activity patterns and convert them into a change in a concentration of a specific molecule, or to a chemical reaction. This section describes the changes in synapses that enable long-term synaptic plasticity, a phenomenon called *expression*. Expression refers to the events downstream of Ca^{2+} influx and the ways in which transient changes in postsynaptic Ca^{2+} levels translate to long-lasting changes in synaptic efficacy.

Mechanisms for the expression of synaptic plasticity are modifications of the mechanisms that determine synaptic strength (Chapters 15, 16 and 17). Plasticity could be expressed presynaptically by changes in the probability of transmitter release or postsynaptically by changes in the unitary conductance of synaptic receptors or their number. The two possibilities are not mutually exclusive. It is difficult to directly determine the locus of expression. Therefore, a variety of physiological measurements and analyses have been developed over the years that indirectly determine the expression mechanism and its locus.

Use of Classical Quantal Analysis to Identify Loci of Expression

A change in failure rates (Chapter 15) is one method to determine the site of expression of synaptic plasticity. The relationship between an action potential and transmitter release is not one-to-one; an event in which release does not occur is called a failure. If the probability that an action potential triggers a release event that elicits a postsynaptic response is p, then the probability that an action potential will fail to drive a postsynaptic response is given by $(1 - p)$. For k independent release sites the probability of a transmission failure between the two cells is: $(1 - p)^k$. A presynaptic mechanism would change p. Figure 18.8 illustrates two examples, one of a presynaptic mechanism in which p changes (Fig. 18.8A) and a second of a postsynaptic mechanism in which p does not change but the magnitude of a successful transmission event changes (Fig. 18.8B). If an average is made over many such experiments, as seen in the bottom panels of the figure, it is difficult to distinguish between these two different mechanisms. However, the differences are evident by observing single events (Figs.18.8A1 and 18.8B1). If a presynaptic mechanism is applicable, then p changes and the probability of failure is reduced after LTP, as seen in Fig. 18.8A1. By contrast, a postsynaptic mechanism will change the magnitude of the postsynaptic potential, but not the probability of failure (Fig. 18.8B1).

Another method for assessing whether expression is pre- or postsynaptic is to calculate the coefficient of variation (CV) of the evoked potentials. This approach was introduced in Chapter 15 and in Box 15.4, where the assumptions and the simplifications underlying this analysis are described. The equation for CV typically used in this analysis is:

$$CV = \sqrt{(1 - p)/kp}$$

According to this equation, CV is determined by presynaptic behavior. As shown in Figure 18.8, presynaptic LTP (Fig 18.8A2) reduces CV, as would be predicted for an increase in p, whereas postsynaptic LTP (Fig 18.8B2), which should have no effect on presynaptic processes, has no effect on CV. The CV method has the advantage over the failure method that it is not necessary to record failures, which are often rare and difficult to record at CNS synapses. The validity of each method is dependent on a number of assumptions that are described in Chapter 15.

Long-term plasticity may also cause changes to short-term plasticity. As presented earlier in this chapter, it is often the case that short-term synaptic depression arises due to vesicle depletion. If LTP is expressed via an increase in neurotransmitter release, this would be expected to cause an acceleration of vesicle depletion. Therefore, presynaptic LTP should increase short-term depression, and decrease short-term facilitation, or even convert a facilitating synapse to a depressing synapse (Markram and Tsodyks, 1996).

Despite the elegance of the above methods, their implementation has yielded conflicting results. For example, in CA1 synapses, some experiments support a postsynaptic expression locus by showing no change in failures or CV, whereas other experiments support a presynaptic expression locus by showing a change in

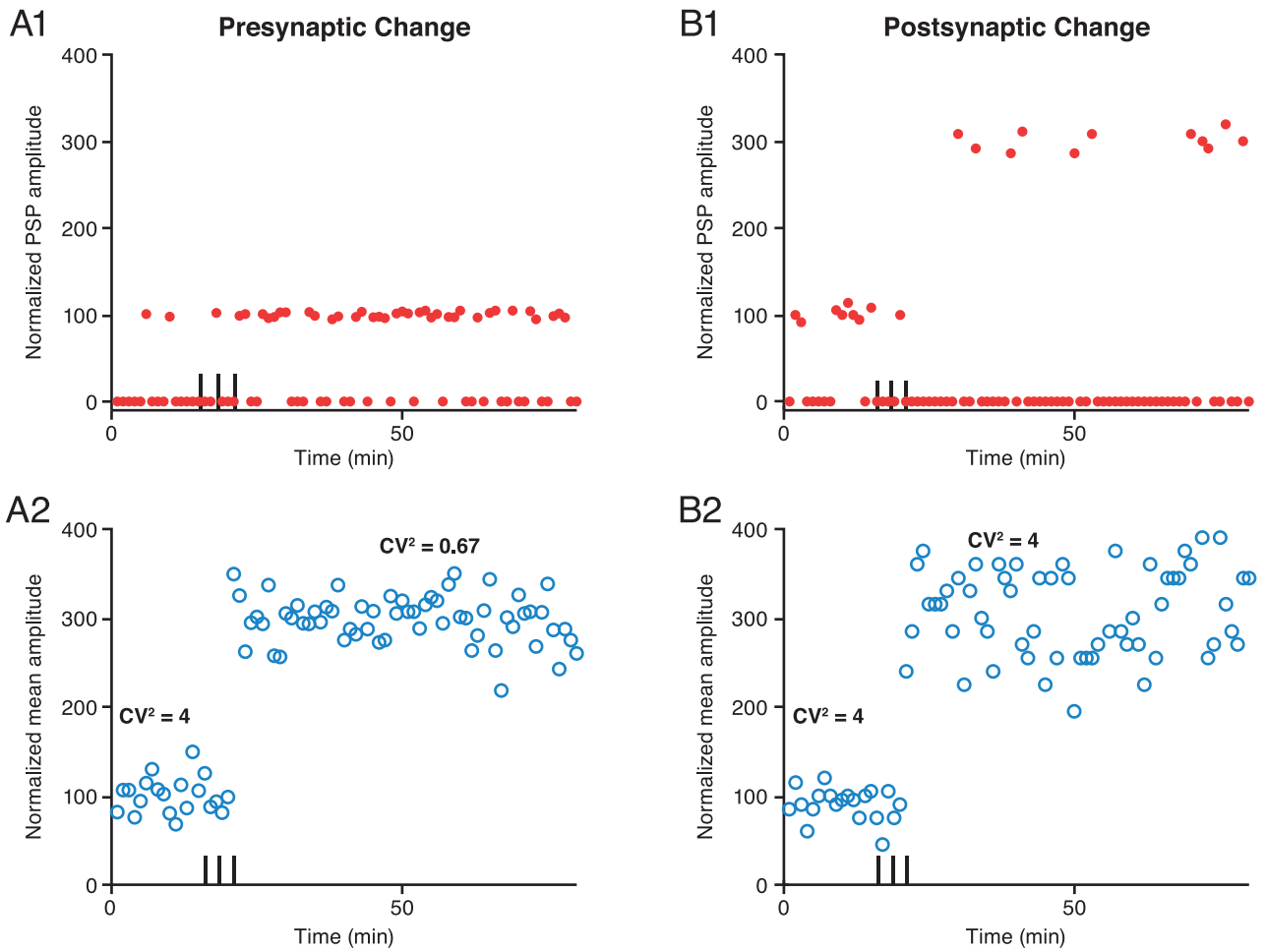

FIGURE 18.8 **Determination of expression mechanism with minimal stimulation.** Often plasticity is represented as the mean postsynaptic potential, averaged over many repetitions or experiments. This is a convenient representation because synaptic transmission is noisy and averaging reduces the variability in the presentation. However, such averaged results can look nearly identical regardless of the locus of expression. Examination of single transmission events can be useful in revealing the locus of expression. Here, schematic images of synaptic transmission before and after LTP are shown. The timing of the stimulus that induces LTP is represented by the three vertical lines. (A1) Presynaptic LTP increases the probability that a PSP will occur but does not affect the magnitude of the individual PSP. In this example, the probability of release was increased from 0.2 to 0.6. (A2) The magnitude of the average PSP increases after LTP due to the increased release probability, while the CV decreases. (B1) In postsynaptically expressed LTP, the probability of release does not change, but the magnitude of each individual PSP is enhanced. In this example, the probability of release was held constant at 0.2. (B2) The magnitude of the average PSP increases, as in the case of a presynaptic locus of expression, however the calculated CV is not altered.

failures and CV. Such apparent discrepancies may result from subtle differences in the way the experiments are performed. For example, the temperature of the neuronal slice during the recording, the ionic composition of the artificial cerebrospinal fluid in which the slice is bathed, the age of the animal from which the slice is obtained and the exact details of the induction protocols, such as the frequency and duration of the stimulus, can all potentially affect the outcome. In addition, one must consider that the experimental conditions in a slice preparation will not exactly match the conditions that occur within the animal. That results are sensitive to experimental conditions suggests that a variety of expression mechanisms may coexist in synapses and that different ones are used under different circumstances.

Evidence for Postsynaptic Expression Mechanisms for LTP

One feature of CNS synaptic transmission that can explain, at least in part, the contradictory results described previously is the silent synapse (Liao et al., 1995). Assume that stimulation of presynaptic afferents to the recorded neuron activates several synapses (Fig. 18.9). Some of these synapses have both AMPA and NMDA receptors, whereas others have only NMDA receptors; the latter are called silent synapses because when the cell is at rest, the NMDARs do not allow a

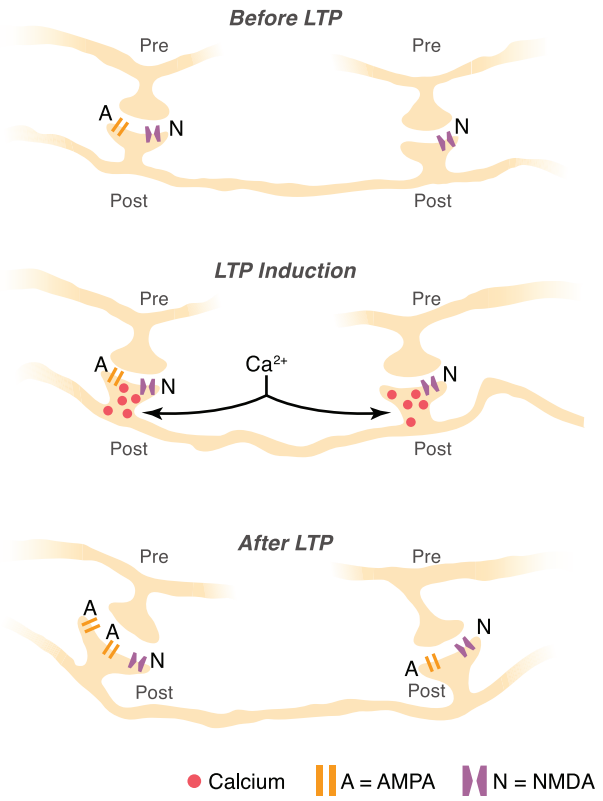

FIGURE 18.9 **Expression of LTP via insertion of AMPA receptors.** Before the induction of synaptic plasticity (top panel) some synapses have both AMPA and NMDA receptors whereas others have only NMDA receptors. Synapses with NMDA receptors only are called silent synapses because NMDA receptors do not conduct significant current near the resting membrane potential. During the induction of LTP (middle panel), Ca^{2+} enters the spines through the NMDA receptors, which trigger the expression of synaptic plasticity. After the induction of LTP (bottom panel), AMPA receptors are added to silent synapses; rendering them much stronger and no longer silent. AMPA receptors are also added to synapses that previously had both AMPA and NMDA receptors.

significant amount of current to pass into the postsynaptic cell because at the resting potential their pores are blocked by Mg^{2+} ions. Under such conditions, when the presynaptic axon is stimulated, neurotransmitter released at a silent synapse will be perceived as a failure. However, if the postsynaptic cell is depolarized at the time of the stimulus, such as by AMPAR activation, the Mg^{2+} block of the NMDARs will be relieved, the NMDARs will conduct, and the response to the stimulus will be recorded as a success. LTP, according to this explanation, triggers an insertion of AMPA receptors into these previously silent synapses (AMPAfication). These synapses now respond, causing an apparent increase in the presynaptic probability of release. In reality, however, the mechanism is postsynaptic in origin.

Other support for a postsynaptic expression locus for LTP comes from studies in which the possible contribution of presynaptic changes were bypassed by the focal uncaging of glutamate near a synapse via a well-focused pulse of UV-laser light (Bagal et al., 2005). Long-term plasticity was induced by pairing such uncaging-induced synaptic activation with postsynaptic depolarization. This protocol produced LTP that could not be accounted for by presynaptic changes because the presynaptic terminal was not stimulated, and thus, only changes in postsynaptic sensitivity could affect responses to glutamate uncaging.

Additional direct support comes from the growing knowledge of the postsynaptic molecular mechanisms of expression. The postsynaptic expression of synaptic plasticity in hippocampal CA1 synapses depends upon both the trafficking and the phosphorylation of AMPA receptors. AMPA receptors are heteromers usually composed of GluR2 receptors in combination with either GluR1 or GluR3 (in different developmental stages and systems the composition might differ). The induction of LTP causes phosphorylation of GluR1 receptors at a site selective to CaMKII (Lee et al., 2003). This phosphorylation causes an increase in the conductance of this receptor (Benke et al., 1998; Derkach et al., 1999), but possibly more importantly, it increases the trafficking of such receptors to the postsynaptic membrane, thus increasing their surface expression and the total synaptic conductance (Shi et al., 2001; Malinow and Malenka, 2002). The trafficking of GluR2 receptors does not depend on the induction of LTP, and they seem to be constitutively trafficked to and from the receptor membrane. During the induction of phase of LTP, GluR1 receptors are rapidly trafficked to synapses in a phosphorylation-dependent manner. Subsequently, GluR2 receptors replace these more transient GluR1 receptors, sustaining the increase in synaptic conductance. By contrast, the induction of LTD causes activation of phosphatases and the dephosphorylation of GluR1 receptors at a PKA site (Lee et al., 2003), and also phosphorylation of GluR2 receptors (Kim et al., 2001). The dephosphorylation of AMPA receptors leads to a reduction in synaptic current by both reducing single channel conductance (Banke et al., 2000) and increasing receptor endocytosis. However, the well-established notion (Malinow and Malenka, 2002) that some AMPA receptors subtypes, such as GluR1, are necessary for and play a special role in the expression of synaptic plasticity has been challenged by recent findings (Granger et al., 2013).

Evidence for Presynaptic Expression Mechanisms for LTP

Despite significant evidence for postsynaptic expression of long-term synaptic plasticity, newer investigative approaches, such as the use of optical methods that allow for the examination of single synapses, have revealed that the expression of long-term plasticity can be accompanied by changes in neurotransmitter

release from presynaptic terminals. In one series of experiments, stimulus-evoked Ca^{2+} transients in single postsynaptic spines were used both as an index of synaptic transmission and to estimate the probability of neurotransmitter release (Emptage et al., 2003; Enoki et al., 2009). These experiments revealed changes in single synapse failure rates, most parsimoniously interpreted as an increase in the presynaptic probability of release. Moreover, it was concluded that a decrease in failure rates could account for most of the LTP observed in these experiments. In another set of experiments, the release probability of CA1 synapses was compared before and after LTP induction (Zakharenko et al., 2001). This feat was accomplished by labeling synaptic vesicles with the styryl dye FM1-43 and using the fluorescence signal as a reporter of vesicle fusion and neurotransmitter release (Chapter 15). Each vesicle that fuses with the plasma membrane during exocytosis slightly decreases the florescence signal, and therefore an increased release probability would result in a faster decrease in fluorescence. The results demonstrated that LTP induced by a 200-Hz tetanus indeed increases the probability of release. Further experiments have shown that the increase in release probability is due to the increasing contribution of N-type voltage gated Ca^{2+} channels to vesicle fusion (Ahmed and Siegelbaum, 2009).

These results seem to indicate that at least under certain conditions a presynaptic locus of expression is possible, even in CA1 synapses. This seems to be inconsistent with the commonly held view that LTP in CA1 synapses is expressed postsynaptically, a view promoted by the more extensive understanding of mechanisms of postsynaptic expression. As noted earlier, such apparent inconsistencies might indicate that small changes in protocol, for example, age, stimulation paradigm, or the presynaptic pathway stimulated, change the locus of expression. These seemingly very different experimental results and their interpretation might also favor a more balanced interpretation of experimental data in which pre- and postsynaptic changes coexist (Bliss and Collingridge, 2013).

Here, we have concentrated on expression mechanisms of LTP in CA1; however, in mossy fiber synapses within the hippocampus both LTP and LTD are expressed presynaptically (Nicoll and Malenka, 1995). Synaptic plasticity has been observed in many different areas, cells and synapses, and both pre- and postsynaptic loci of expression have been observed in different systems.

LTD Expression Mechanisms

Expression mechanisms for LTD have not been investigated as extensively as those for LTP. In CA1 synapses there is significant evidence of a postsynaptic mechanism, and like for LTP, both phosphorylation and trafficking or receptors are indicated (Malenka and Bear, 2004). It is clear, however, that mechanisms of expression differ in different systems. For example, some well-documented forms of neocortical LTD seem to have presynaptic expression mechanisms (Sjöström et al., 2003; Bender et al., 2006) and even within the same cortical area, different synapses might have different expression and induction mechanisms depending upon the developmental stage, the cortical layer and possibly the types of target neurons (Crozier et al., 2007; Larsen et al., 2010).

Role of Morphological Changes in Expression of LTP and LTD

The induction of LTP is accompanied by the enlargement of synaptic spines (Harris et al., 2003; Matsuzaki et al., 2004). However, there is no general consensus as to whether such structural changes are the cause or the consequence of synaptic plasticity, for how long the structural changes persist and if long-term plasticity can be expressed without these structural changes (Alvarez and Sabatini, 2007). Thus structural plasticity may be a good anatomical indicator of plasticity, but its functional significance or the mechanisms responsible for such structural plasticity are unclear.

Maintenance of Long-Term LTD and LTP

Memories that can last a lifetime are expressed by changes in the number or conformational states of synaptic proteins. Yet, synaptic proteins themselves have a much shorter lifetime than the lifetime of memories, and due to diffusion and trafficking, the dwell time of these proteins in synapses is even more limited. Francis Crick raised this fundamental problem of maintenance in 1984 (Crick, 1984). Since then various options to account for this long-lasting phase of synaptic plasticity, the maintenance phase, have been examined, but as of yet there is no agreed upon resolution of this fundamental problem.

Like memory, long-term synaptic plasticity can last for extended periods of time, as one would expect of the substrate of memory. LTP induced *in vitro* is limited to hours because of the limited lifetime of the preparation. However, *in vivo* LTP has been observed to persist for at least one week and conceivably longer than recordings can be maintained (Staubli and Lynch, 1987; Abraham et al., 1993). Not all induction protocols cause such a long-lasting LTP. For example, a weak stimulus consisting of a single tetanus can induce the maximal level of LTP, but this LTP decays within 2–4 hours. However, LTP induced by three such tetanic bursts can last for the lifetime of the slice (up to

~12 hours); such long-lasting LTP is called late-LTP (L-LTP). Similarly, there is also a long-lasting form of LTD, L-LTD. This late phase of synaptic plasticity is also called the maintenance phase. In order to understand the stability of synaptic plasticity and memory, it is necessary to gain an understanding of the mechanisms enabling maintenance.

Protein Synthesis is Essential for the Maintenance of LTD and LTP

A possible key for understanding maintenance is that both L-LTP and L-LTD depend on the synthesis of new proteins (see Chapter 5). If the synthesis of new proteins is blocked during the induction protocol and for about 30 min after the induction protocol, LTP or LTD are established, but plasticity decays within 2–4 h (Frey et al., 1988; Abraham and Williams, 2008). Similarly long-term memory also depends on protein synthesis (Davis and Squire, 1984). Curiously, if protein synthesis is blocked at a later stage, for example a few hours after the induction of L-LTP, there is no apparent reversal of L-LTP (Frey et al., 1988). Thus, maintenance seems to depend upon the production of new proteins during and shortly after the induction phase. This process by which the translation of new proteins is essential for maintenance is sometimes called consolidation and takes place over a limited time window. However, proteins have a limited lifetime. Furthermore, a protein could potentially diffuse and traffic throughout the cell, causing the dwell-time of the protein in a particular location, such as at a potentiated synapse, to be shorter than its overall lifetime. The dwell-times of synaptic proteins naïvely sets an upper time limit on maintenance; conceivably this could be extended by the synthesis of new proteins. However, the observations indicating a lack of effect of the application of protein synthesis inhibitors during the maintenance phase seem to indicate that maintenance itself does not depend on the production of new proteins during the late phase (see however Aslam et al., 2009, Zhang et al., 2010). Therefore, these observations do not seem to address fully the central problem of maintenance.

When Crick raised the problem of maintenance, he also suggested that some form of cooperativity between synaptic proteins could resolve this dilemma. Soon thereafter, John Lisman (1985) suggested that this abstract cooperativity could be embodied by autophosphorylation of some plasticity-related kinases (Lisman, 1985). He suggested that such autophosphorylation could form a bistable switch that is robust to protein turnover. This putative protein was subsequently mapped onto the CaMKII kinase, a kinase highly abundant in synapses and essential for the induction of LTP. Detailed computational models of the autophosphorylation in CaMKII holoenzymes (Lisman and Zhabotinsky, 2001; Miller et al., 2005) have shown that this can indeed be a bistable system. However, now nearly 30 years after this hypothesis was put forward, there is no significant evidence indicating that L-LTP causes a prolonged increase in the phosphorylation of CaMKII. Inhibition of CaMKII does not reverse L-LTP during the maintenance phase (Otmakhov et al., 1997, but see Sanhueza et al., 2007), and *in vitro* CaMKII autophosphorylation does not generate a bistable loop (Bradshaw et al., 2003). In addition, this idea does not explain the significance of protein synthesis during the induction of L-LTP or memory formation.

Bistability Based on Local Protein Synthesis

Protein synthesis of specific genes can be turned on or off in a long-lasting or permanent manner, and this is often accomplished via a positive feedback loop between a protein and transcription factors that control the transcription of specific genes. However, such a process might be expected to up- or downregulate the level of a specific protein in a cell-wide manner. Therefore, this mechanism could not, by itself, account for the specific upregulation of proteins at some synapses and not others (synapse specificity). However, the control of protein synthesis could be at the level of translation rather than transcription. In neurons, polyribosomes and some specific mRNAs are found locally in dendrites and even within synaptic spines (Steward and Levy, 1982; Ostroff et al., 2002), and there is evidence that local dendritic protein synthesis is required for long-term plasticity (Sutton and Schuman, 2006; see also Chapter 5). Thus, the control of translation could be local and even synapse specific. Consequently, bistability that can compensate for protein turnover and at the same time is synapse specific could be implemented at the level of translation (Klann and Sweatt, 2008). One possible specific mechanism for implementing this bistable switch is the translation of CaMKII and the cytoplasmic polyadenylation element-binding protein 1 (CPEB1) (Wells et al., 2001), which controls the translation of CaMKII. The feedback loop is closed because CaMKII controls the activity of CPEB1 via phosphorylation. A computational model has shown that this feedback loop at the level of new protein translation can be bistable, and surprisingly, can explain the differential effect of protein synthesis inhibitors in the early and late phases of LTP (Aslam et al., 2009). Although this model is based on the CaMKII protein, its assumptions and consequences are significantly different from the CaMKII autophosphorylation model. One different consequence is that in the local synthesis model, the total amount of CaMKII changes after L-LTP, whereas the fraction phosphorylated does not change much. Although these consequences are consistent with experiments, there is as yet no strong

experimental evidence to support the involvement of CaMKII or CPEB1 in long-term plasticity or memory beyond the scale of several hours.

Maintenance Based on Synthesis of an Atypical Protein Kinase C

The simplest way to test if a protein or a set of proteins is involved in maintenance is to block their activity during the maintenance phase of memory or synaptic plasticity and see that a previous memory or previously established plasticity is reversed. The protein for which there is best evidence of this form is the atypical protein kinase Cζ (PKCζ) or more specifically the constitutively active form of this protein PKMζ. The same gene encodes both of these proteins, but the PKMζ form is translated without the regulatory subunit and therefore is constitutively active. Several pharmacological inhibitors block PKMζ activity; most prominent of these is the zeta inhibitory peptide (ZIP). Inhibitors of PKMζ can reverse plasticity and various forms of memory long after plasticity and memory have been established (Sacktor et al., 1993; Pastalkova et al., 2006; Shema et al., 2007; Sacktor, 2011). In addition to blocking memory with inhibitors of PKMζ, inducing long-term plasticity or memory produces an increase in the concentration of PKMζ. This increase in concentration is consistent with the idea that PKMζ is involved in memory maintenance and is also consistent with results indicating the importance of protein synthesis for L-LTP, because new PKMζ is synthesized when long-term memory is established.

If PKMζ is indeed the "memory molecule" the same question still remains: how can memory be stable in the face of protein turnover, diffusion and trafficking? One possibility is that PKMζ is a special molecule that does not degrade, diffuse, or traffic. Another option is that it is part of a bistable protein network, where bistability arises from reactions similar to those discussed above. Several computational models have explored this option (Ogasawara and Kawato, 2010; Zhang et al., 2010; Smolen et al., 2012).

Recently, doubts have been cast on the PKMζ theory of maintenance, as mutant mice that lack the PKCζ gene can still establish long-term plasticity and memory (Lee et al., 2013; Volk et al., 2013). Surprisingly, in these same mice, ZIP still reverses established memory. This result indicates that ZIP is not solely selective to PKMζ, and more importantly raises the question of the identity of the substrate upon which ZIP acts to reverse memory. It is known that ZIP also inhibits a similar protein, PKCλ/ι, and that this protein is also activated during synaptic plasticity (Ren et al., 2013). Therefore, a simple explanation is that PKCλ/ι is responsible for memory maintenance. Alternatively, there may be redundancy such that either PKCλ/ι or PKMζ can maintain memory.

Although it is sufficient to block translation during the induction phase of L-LTP in order to prevent L-LTP, transcriptional regulation is also important during the induction of L-LTP and long-term memory (Abel et al., 1997). The importance of transcription for long-term forms of memory has been better studied in *Aplysia*, as described in the next section. However, some of the proteins involved in long-term memory in *Aplysia*, specifically CREB1 and CREB2, seem to also play some role in L-LTP in the CA1 region and in long-term memory. Note that transcriptional regulation is a whole-cell phenomenon and thus it alone cannot account for the maintenance of synapse specific L-LTP. However, persistent changes in transcription can be permissive for L-LTP, or might be involved in altering the ability of the cell to undergo subsequent synaptic plasticity, a phenomena called metaplasticity.

An alternative idea for the mechanism of maintenance presented by Si et al. (2003) suggests that a CPEB subtype in *Aplysia* has prion-like properties, which might be responsible for maintenance (Si et al., 2003). This idea, which was explored primarily in the context of long-term facilitation in *Aplysia*, is described in the next section.

Although L-LTP is synapse specific, the activation of maintenance is not necessarily synapse specific. As noted above a strong stimulus can evoke homosynaptic L-LTP whereas a weak stimulus evokes LTP, which decays within a few hours. However, if one synapse is strongly activated, other synapses that are only weakly stimulated may also develop L-LTP (Frey and Morris, 1997; Frey and Morris, 1998). The time window between the long and weak activation can be as long as a few hours in both directions. This phenomenon, first characterized in rodent hippocampus, but later found in *Aplysia* (Casadio et al., 1999), has been termed synaptic tagging. The mechanistic basis of synaptic tagging is not fully clear (Martin and Kosik, 2002). However, it is thought that once plasticity (weak or strong) is induced in a synapse, a tag is established within that synapse that can last for a few hours. A strong stimulus causes the synthesis of those proteins necessary for L-LTP, which diffuse throughout the cell. Synaptic tags can capture these newly synthesized proteins and use them to convert LTP to L-LTP.

Long-Term Heterosynaptic Facilitation

Although LTP and LTD in CA1 neurons is usually characterized as homosynaptic, heterosynaptic plasticity has also been observed. For example, the *in vivo* induction of LTP of the perforant path can induce LTD in the

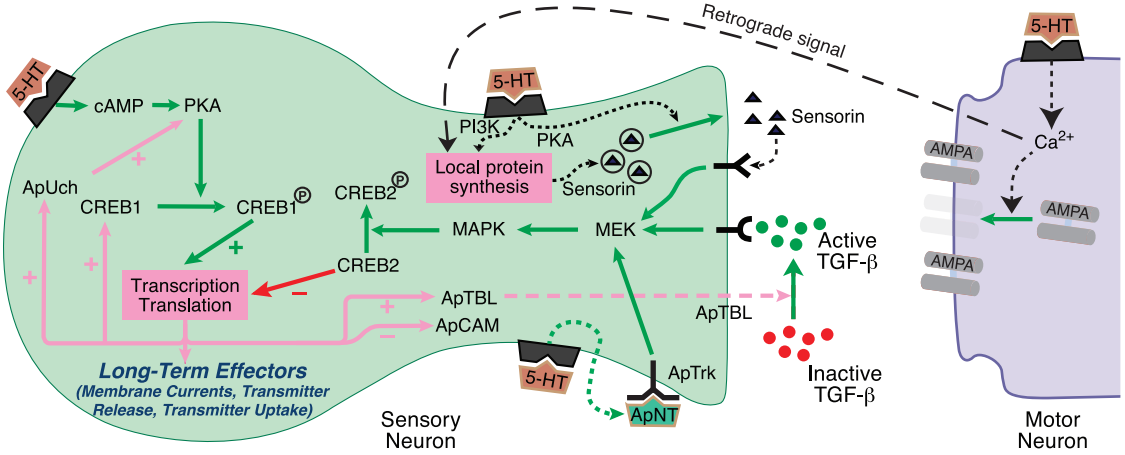

FIGURE 18.10 **Simplified scheme of the mechanisms in SNs that contribute to long-term heterosynaptic facilitation.** Serotonin leads to cAMP-dependent regulation of CREB1 and also leads to activation of MAPK, which regulates CREB2. Whereas CREB1 acts as an initiator of gene transcription, CREB2 acts as a repressor of gene transcription. The combined effects of activation of CREB1 and suppression of CREB2 lead to regulation of the synthesis of at least 10 proteins, only some of which are shown. ApTBL is believed to activate latent forms of TGF-β, which can then bind to receptors on the SN. TGF-β activates MAPK, which may act by initiating a second round of gene regulation by affecting CREB2-dependent pathways. Serotonin can also increase the release of the peptide sensorin, which binds to autoreceptors leading to further activation of MAPK. Increased local synthesis and subsequent release of sensorin can also be evoked by 5-HT, through the PI3 kinase and type II PKA, respectively. Because increased synthesis of sensorin requires elevation of postsynaptic Ca^{2+}, a retrograde signal is also postulated. In addition to the retrograde signal, 5-HT-induced postsynaptic signaling also leads to an increased number of glutamate receptors.

nonstimulated control pathway (Abraham et al., 1985; Christie and Abraham, 1992; Doyere et al., 1997). This heterosynaptic plasticity is NMDAR dependent, but the mechanism responsible for it is not well understood—partially because it is difficult to produce an analog of the procedure in slices.

In the *Aplysia* sensorimotor synapse, heterosynaptic facilitation also exists in a long-term form (LTF), which persists for at least 5 days. Whereas short-term facilitation (STF) can be produced by a single brief application of 5-HT, the induction of LTF requires multiple stimuli spaced over an approximately one-hour period.

Both STF and LTF share some common cellular pathways during their *induction*. For example, both forms activate the cAMP/PKA cascade (Figs. 18.4, 18.10). However, in the long-term form, unlike the short-term form, activation of the cAMP/PKA cascade induces gene transcription and new protein synthesis (Kandel, 2001). Repeated training leads to a translocation of PKA to the nucleus where it phosphorylates the transcriptional activator CREB1 (cAMP responsive element binding protein). CREB1 binds to a regulatory region of genes known as CRE (cAMP responsive element). Whereas CREB1 acts as an *activator* of gene transcription, a related transcription factor, CREB2, acts constitutively as a *repressor* of gene transcription. This repression of transcription is in turn *suppressed* by MAPK phosphorylation of CREB2 (Bartsch et al., 1998; Guan et al., 2002). MAPK is activated by multiple pathways including a neurotropin (ApNT) sensitive tyrosine receptor kinase receptor (ApTrk), and through feedback pathways involving the peptide sensorin and transforming growth factor β (TGF-β) (see below). As for LTP (see above), individual synapses of sensory neurons are marked or tagged so they can capture the newly synthesized proteins (Casadio et al., 1999).

The role of transcription factors in long-term memory formation is not limited to the induction phase but may also extend to the consolidation phase, where consolidation is defined as the time window during which RNA and protein synthesis are required for converting short- to long-term memory. For example, treatment of ganglia with five pulses of 5-HT over a 1.5 h period to mimic sensitization training leads to the binding of CREB1 to the promoter of its own gene and induces CREB1 synthesis. The necessity of prolonged transcription and translation for LTF observed 24 h after treatment persists for at least 10 h after induction. These results suggest that CREB1 can regulate its own level of expression, giving rise to a CREB1 positive feedback loop that supports memory consolidation (Liu et al., 2011).

The combined effects of activation of CREB1 and removal of CREB2's repression of transcription lead to changes in the synthesis of specific proteins. So far, more than 10 gene products that are regulated by 5-HT have been identified, and others are likely to be found in the future. These results indicate that there is not a single plasticity gene or protein, but that multiple genes are regulated, and they act in a coordinated way to alter neuronal properties and synaptic strength. The following section discusses several regulated proteins of particular significance.

The downregulation of a homolog of a neuronal cell adhesion molecule (NCAM), denoted ApCAM plays a key role in long-term facilitation. This downregulation has two components. First, the synthesis of ApCAM is reduced. Second, preexisting ApCAM is internalized via increased endocytosis. The internalization and degradation of ApCAM allow for the restructuring of the axon arbor (Bailey and Kandel, 2008). The sensory neurons (SN) can now form additional connections with the same postsynaptic target or make new connections with other cells. In addition, the presynaptic cell-adhesion protein neurexin, along with its postsynaptic counterpart neuroligin and their transsynaptic interaction, are required for 5-HT-induced LTF and the associated presynaptic structural changes (Choi et al., 2011). Furthermore, the stabilization of new structures depends on a translation-regulating protein, the *Aplysia* homolog of CPEB (ApCPEB; Miniaci et al., 2008). ApCPEB, as mentioned in the section on LTP, appears to have prion-like properties in that it can appear in one of two or more conformations, one of which dominates and allows ApCPEB to self-perpetuate. Conversion of ApCPEB to the self-perpetuating state is enhanced by 5-HT and required for the persistence of LTF (Si et al., 2010). Finally, the persistence of LTF and sensitization can be disrupted by inhibition of an *Aplysia* homolog of protein kinase M (PKM Apl III; Cai et al., 2011).

Another protein whose synthesis is regulated by long-term facilitation is *Aplysia* tolloid/BMP-like protein (ApTBL-1). Tolloid and the related molecule BMP-1 appear to function as secreted Zn^{2+} proteases. In some systems, they activate members of the transforming growth factor β (TGF-β) family. Indeed, in SNs, TGF-β mimics the effects of 5-HT in that it produces long-term increases in the synaptic strength of the SNs (Zhang et al., 1997). Interestingly, TGF-β activates MAPK in the SNs and induces its translocation to the nucleus. Thus, TGF-β could be part of an *extracellular* positive feedback loop, possibly leading to another round of protein synthesis (Fig. 18.10) to further consolidate the memory (Zhang et al., 1997). Another extracellular positive feedback loop involves the 5-HT-induced regulation of the release of the SN-specific neuropeptide sensorin (Fig. 18.10). Synthesis of sensorin is stimulated by 5-HT in a PI3 kinase (phosphatidylinositol 3-kinase)-dependent manner and requires elevation of postsynaptic Ca^{2+} (Hu et al., 2006; Cai et al., 2008). The mechanism through which postsynaptic Ca^{2+} regulates presynaptic local protein synthesis of sensorin remains unclear, but the release of a retrograde signal has been postulated (Cai et al., 2008). Interestingly, although the existence of a postsynaptic neuron seems to be required for long-term facilitation, it is not required for another correlate of long-term sensitization, increased SN excitability (Dale et al., 1987; Cleary et al., 1998; Liu et al., 2011). Sensorin binding to presynaptic autoreceptors activates MAPK (Hu et al., 2006), which phosphorylates CREB2 and contributes to transcriptional regulation during the consolidation of LTF. Finally, 5-HT leads to the activation of a Trk receptor and subsequent activation of MAPK (Purcell et al., 2003; Ormond et al., 2004; Sharma et al., 2006). This additional feedback loop is mediated at least in part by an endogenous *Aplysia* neurotrophin (ApNT) (Kassabov et al., 2013).

Yet another important protein, *Aplysia* ubiquitin hydrolase (ApUch), appears to be involved in an *intracellular* positive feedback loop (Fig 18.10). A central pathway through which selective proteins are degraded involves the ubiquitin-proteosome pathway (UPS) (Hegde and Diantonio, 2002). This process is highly regulated by many enzymes, including deubiquitinating enzymes. By removing ubiquitin from proteins prior to their degradation, deubiquitinating enzymes could promote recycling of ubiquitin and facilitate processing through the UPS (Wing, 2003). During the induction of LTF, ApUch levels in SNs are increased, possibly via CREB phosphorylation and a consequent increase in *ApUch* transcription. The increased levels of ApUch increase the rate of degradation of proteins, via the UPS, including the regulatory subunit of PKA (Chain et al., 1999). The catalytic subunit of PKA, when freed from the regulatory subunit, is highly active. Thus, increased ApUch will lead to an increase in PKA activity and a more protracted phosphorylation of CREB1. This phosphorylated CREB1 may act to further prolong *ApUch* expression, thus closing a positive feedback loop. Protein degradation, in general, and the role of ubiquitination in particular, is an emerging theme in recent studies on the neural basis of long-term memory (see next section and Fioravante and Byrne, 2011).

Long-Term Heterosynaptic LTD in Aplysia

In *Aplysia*, the endogenous tetrapeptide Phe-Met-Arg-Phe-NH_2 (FMRFa) induces transcription- and translation-dependent LTD at the connection between sensory neurons and motor neurons (Montarolo et al., 1988; Bailey et al., 1992). FMRFa leads to activation of p38 MAPK (mitogen-activated protein kinase), which is necessary for LTD (Guan et al., 2003; Fioravante et al., 2006). FMRFa also promotes structural changes, including loss of presynaptic varicosities and retraction of neurites (Schacher and Montarolo, 1991). The structural rearrangements appear to depend on selective protein degradation, as they do in several other examples of long-term plasticity (Bingol and Schuman, 2005). As described in the section on LTF, a key component of the UPS that is involved in the upregulation of LTF in *Aplysia* is ApUch (Hegde et al., 1997). Interestingly, *ap-Uch* is a target gene that is upregulated during LTD at least partly in a p38 MAPK-

dependent manner. This upregulation is likely mediated by CREB2, which is traditionally regarded as a transcription repressor (see section on LTF). CREB2 is phosphorylated during LTD at a putative MAPK site and this phosphorylation of CREB2 is necessary for LTD (Fioravante et al., 2008).

Summary II

Long-term synaptic plasticity is a key mechanism underlying the formation and regulation of neuronal circuits (Malenka and Bear, 2004) and long-term memory (see Chapter 20). LTP at the CA3-CA1 synapse and LTF at the *Aplysia* sensorimotor synapse have been particularly well studied. Long-term plasticity can be broken down into separate phases: induction, expression and maintenance. The induction mechanisms vary, but a common theme is the activation of second messenger systems either by Ca^{2+} or modulatory transmitters. The expression of synaptic plasticity can either be presynaptic via changes in the probability of release, or postsynaptic via changes in number or properties of AMPA receptors. LTP and LTF persist for long periods of time, a feature that requires special mechanisms such as the synthesis of new proteins, and possibly on specific molecular networks local to each synapse, which can maintain the synaptic efficacy despite protein turnover and diffusion.

Long-term plasticity is universal, occurring at different synapses from the spinal cord (Woolf and Salter, 2000) to the neocortex, and in animals ranging from invertebrates (Lin and Glanzman, 1994) to humans (Cooke and Bliss, 2006). However, diversity is observed in the induction and expression mechanisms such that even synapses on adjacent neurons in the same cortical areas can be induced and expressed via different mechanisms (Crozier et al., 2007). Future studies will be required to elucidate the functional significance of these different induction and expression mechanisms.

References

Abbott, L.F., Regehr, W.G., 2004. Synaptic computation. Nature. 431, 796–803.

Abbott, L.F., Varela, J.A., Sen, K., Nelson, S.B., 1997. Synaptic depression and cortical gain control. Science. 275, 220–224.

Abel, T., Nguyen, P.V., Barad, M., Deuel, T.A., Kandel, E.R., Bourtchouladze, R., 1997. Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory. Cell. 88, 615–626.

Abraham, W.C., Bliss, T.V., Goddard, G.V., 1985. Heterosynaptic changes accompany long-term but not short-term potentiation of the perforant path in the anaesthetized rat. J. Physiol. 363, 335–349.

Abraham, W.C., Mason, S.E., Demmer, J., Williams, J.M., Richardson, C.L., Tate, W.P., et al., 1993. Correlations between immediate early gene induction and the persistence of long-term potentiation. Neuroscience. 56, 717–727.

Abraham, W.C., Williams, J.M., 2008. LTP maintenance and its protein synthesis-dependence. Neurobiol. Learn. Mem. 89, 260–268.

Ahmed, M.S., Siegelbaum, S.A., 2009. Recruitment of N-Type Ca^{2+} channels during LTP enhances low release efficacy of hippocampal CA1 perforant path synapses. Neuron. 63, 372–385.

Alford, S., Grillner, S., 1991. The involvement of GABAB receptors and coupled G-proteins in spinal GABAergic presynaptic inhibition. J. Neurosci. 11, 3718–3726.

Alle, H., Geiger, J.R., 2007. GABAergic spill-over transmission onto hippocampal mossy fiber boutons. J. Neurosci. 27, 942–950.

Alvarez, V.A., Sabatini, B.L., 2007. Anatomical and physiological plasticity of dendritic spines. Annu. Rev. Neurosci. 30, 79–97.

Angers, A., Fioravante, D., Chin, J., Cleary, L.J., Bean, A.J., Byrne, J.H., 2002. Serotonin stimulates phosphorylation of *Aplysia* synapsin and alters its subcellular distribution in sensory neurons. J. Neurosci. 22, 5412–5422.

Antzoulatos, E.G., Byrne, J.H., 2004. Learning insights transmitted by glutamate. Trends Neurosci. 27, 555–560.

Antzoulatos, E.G., Cleary, L.J., Eskin, A., Baxter, D.A., Byrne, J.H., 2003. Desensitization of postsynaptic glutamate receptors contributes to high-frequency homosynaptic depression of *Aplysia* sensorimotor connections. Learn. Mem. 10, 309–313.

Artola, A., Br√∂Cher, S., Singer, W., 1990. Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. Nature. 347, 69–72.

Aslam, N., Kubota, Y., Wells, D., Shouval, H.Z., 2009. Translational switch for long-term maintenance of synaptic plasticity. Mol. Syst. Biol. 5, 284.

Atluri, P.P., Regehr, W.G., 1996. Determinants of the time course of facilitation at the granule cell to Purkinje cell synapse. J. Neurosci. 16, 5661–5671.

Bagal, A.A., Kao, J.P.Y., Tang, C.-M., Thompson, S.M., 2005. Long-term potentiation of exogenous glutamate responses at single dendritic spines. Proc. Natl. Acad. Sci. U.S.A. 102, 14434–14439.

Bailey, C.H., Kandel, E.R., 2008. Synaptic remodeling, synaptic growth and the storage of long-term memory in *Aplysia*. Prog. Brain Res. 169, 179–198.

Bailey, C.H., Montarolo, P., Chen, M., Kandel, E.R., Schacher, S., 1992. Inhibitors of protein and RNA synthesis block structural changes that accompany long-term heterosynaptic plasticity in *Aplysia*. Neuron. 9, 749–758.

Banke, T.G., Bowie, D., Lee, H.K., Huganir, R.L., Schousboe, A., Traynelis, S.F., 2000. Control of GluR1 AMPA receptor function by cAMP-dependent protein kinase. J. Neurosci. 20, 89–102.

Barber, R.P., Vaughn, J.E., Saito, K., Mclaughlin, B.J., Roberts, E., 1978. GABAergic terminals are presynaptic to primary afferent terminals in the substantia gelatinosa of the rat spinal cord. Brain Res. 141, 35–55.

Bartsch, D., Casadio, A., Karl, K.A., Serodio, P., Kandel, E.R., 1998. CREB1 encodes a nuclear activator, a repressor, and a cytoplasmic modulator that form a regulatory unit critical for long-term facilitation. Cell. 95, 211–223.

Baxter, D.A., Bittner, G.D., Brown, T.H., 1985. Quantal mechanism of long-term synaptic potentiation. Proc. Natl. Acad. Sci. U.S.A. 82, 5978–5982.

Bear, M.F., Kirkwood, A., 1993. Neocortical long-term potentiation. Curr. Opin. Neurobiol. 3, 197–202.

Belardetti, F., Kandel, E.R., Siegelbaum, S.A., 1987. Neuronal inhibition by the peptide FMRFamide involves opening of S K+ channels. Nature. 325, 153–156.

Bender, V.A., Bender, K.J., Brasier, D.J., Feldman, D.E., 2006. Two coincidence detectors for spike timing-dependent plasticity in somatosensory cortex. J. Neurosci. 26, 4166–4177.

Benke, T.A., Lüthi, A., Isaac, J.T.R., Collingridge, G.L., 1998. Modulation of AMPA receptor unitary conductance by synaptic activity. Nature. 393, 793–797.
Bienenstock, E.L., Cooper, L.N., Munro, P.W., 1982. Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. J. Neurosci. 2, 32–48.
Bingol, B., Schuman, E.M., 2005. Synaptic protein degradation by the ubiquitin proteasome system. Curr. Opin. Neurobiol. 15, 536–541.
Bittner, G.D., 1968. Differentiation of nerve terminals in the crayfish opener muscle and its functional significance. J Gen Physiol. 51, 731–758.
Blatow, M., Caputi, A., Burnashev, N., Monyer, H., Rozov, A., 2003. Ca^{2+} buffer saturation underlies paired pulse facilitation in calbindin-D28k-containing terminals. Neuron. 38, 79–88.
Bliss, T.V., Collingridge, G.L., 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 361, 31–39.
Bliss, T.V., Collingridge, G.L., 2013. Expression of NMDA receptor-dependent LTP in the hippocampus: bridging the divide. Mol Brain. 6, 5.
Bliss, T.V., Lomo, T., 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J. Physiol. 232, 331–356.
Bradshaw, J.M., Kubota, Y., Meyer, T., Schulman, H., 2003. An ultrasensitive Ca^{2+}/calmodulin-dependent protein kinase II-protein phosphatase 1 switch facilitates specificity in postsynaptic calcium signaling. Proc. Natl. Acad. Sci. U.S.A. 100, 10512–10517.
Byrne, J.H., Kandel, E.R., 1996. Presynaptic facilitation revisited: state and time dependence. J. Neurosci. 16, 425–435.
Cai, D., Chen, S., Glanzman, D.L., 2008. Postsynaptic regulation of long-term facilitation in *Aplysia*. Curr. Biol. 18, 920–925.
Cai, D., Pearce, K., Chen, S., Glanzman, D.L., 2011. Protein kinase m maintains long-term sensitization and long-term facilitation in *Aplysia*. J. Neurosci. 31, 6421–6431.
Casadio, A., Martin, K.C., Giustetto, M., Zhu, H., Chen, M., Bartsch, D., et al., 1999. A transient, neuron-wide form of CREB-mediated long-term facilitation can be stabilized at specific synapses by local protein synthesis. Cell. 99, 221–237.
Cassenaer, S., Laurent, G., 2007. Hebbian STDP in mushroom bodies facilitates the synchronous flow of olfactory information in locusts. Nature. 448, 709–713.
Castro, A., Aguilar, J., Elias, D., Felix, R., Delgado-Lezama, R., 2007. G-protein-coupled GABAB receptors inhibit Ca^{2+} channels and modulate transmitter release in descending turtle spinal cord terminal synapsing motoneurons. J. Comp. Neurol. 503, 642–654.
Cesca, F., Baldelli, P., Valtorta, F., Benfenati, F., 2010. The synapsins: key actors of synapse function and plasticity. Prog. Neurobiol. 91, 313–348.
Chain, D.G., Casadio, A., Schacher, S., Hegde, A.N., Valbrun, M., Yamamoto, N., et al., 1999. Mechanisms for generating the autonomous cAMP-dependent protein kinase required for long-term facilitation in *Aplysia*. Neuron. 22, 147–156.
Charlton, M.P., Smith, S.J., Zucker, R.S., 1982. Role of presynaptic calcium ions and channels in synaptic facilitation and depression at the squid giant synapse. J Physiol. 323, 173–193.
Chen, G., Harata, N.C., Tsien, R.W., 2004. Paired-pulse depression of unitary quantal amplitude at single hippocampal synapses. Proc. Natl. Acad. Sci. U.S.A. 101, 1063–1068.
Cho, K., Aggleton, J.P., Brown, M.W., Bashir, Z.I., 2001. An experimental test of the role of postsynaptic calcium levels in determining synaptic strength using perirhinal cortex of rat. J. Physiol. 532, 459–466.
Choi, Y.B., Li, H.L., Kassabov, S.R., Jin, I., Puthanveettil, S.V., Karl, K.A., et al., 2011. Neurexin-neuroligin transsynaptic interaction mediates learning-related synaptic remodeling and long-term facilitation in *Aplysia*. Neuron. 70, 468–481.
Christie, B.R., Abraham, W.C., 1992. NMDA-dependent heterosynaptic long-term depression in the dentate gyrus of anaesthetized rats. Synapse. 10, 1–6.
Cleary, L.J., Lee, W.L., Byrne, J.H., 1998. Cellular correlates of long-term sensitization in *Aplysia*. J. Neurosci. 18, 5988–5998.
Coesmans, M., Weber, J.T., De Zeeuw, C.I., Hansel, C., 2004. Bidirectional parallel fiber plasticity in the cerebellum under climbing fiber control. Neuron. 44, 691–700.
Cooke, S.F., Bliss, T.V., 2006. Plasticity in the human central nervous system. Brain. 129, 1659–1673.
Cooper, L.N., Liberman, F., Oja, E., 1979. A theory for the acquisition and loss of neuron specificity in visual cortex. Biol. Cybern. 33, 9–28.
Crick, F., 1984. Memory and molecular turnover. Nature. 312, 101.
Critz, S.D., Baxter, D.A., Byrne, J.H., 1991. Modulatory effects of serotonin, FMRFamide, and myomodulin on the duration of action potentials, excitability, and membrane currents in tail sensory neurons of *Aplysia*. J. Neurophysiol. 66, 1912–1926.
Crozier, R.A., Wang, Y., Liu, C.-H., Bear, M.F., 2007. Deprivation-induced synaptic depression by distinct mechanisms in different layers of mouse visual cortex. Proc. Natl. Acad. Sci. U.S.A. 104, 1383–1388.
Cummings, J.A., Mulkey, R.M., Nicoll, R.A., Malenka, R.C., 1996. Ca^{2+} signaling requirements for long-term depression in the hippocampus. Neuron. 16, 825–833.
Dale, N., Kandel, E.R., 1990. Facilitatory and inhibitory transmitters modulate spontaneous transmitter release at cultured *Aplysia* sensorimotor synapses. J. Physiol. 421, 203–222.
Dale, N., Kandel, E.R., Schacher, S., 1987. Serotonin produces long-term changes in the excitability of *Aplysia* sensory neurons in culture that depend on new protein synthesis. J. Neurosci. 7, 2232–2238.
David, G., Barrett, J.N., Barrett, E.F., 1998. Evidence that mitochondria buffer physiological Ca^{2+} loads in lizard motor nerve terminals. J. Physiol. 509, 59–65.
David, S.V., Mesgarani, N., Fritz, J.B., Shamma, S.A., 2009. Rapid synaptic depression explains nonlinear modulation of spectro-temporal tuning in primary auditory cortex by natural stimuli. J. Neurosci. 29, 3374–3386.
Davies, C.H., Davies, S.N., Collingridge, G.L., 1990. Paired-pulse depression of monosynaptic GABA-mediated inhibitory postsynaptic responses in rat hippocampus. J. Physiol. 424, 513–531.
Davis, H.P., Squire, L.R., 1984. Protein synthesis and memory: a review. Psychol. Bull. 96, 518–559.
Davis, S., Butcher, S.P., Morris, R.G., 1992. The NMDA receptor antagonist D-2-amino-5-phosphonopentanoate (D-AP5) impairs spatial learning and LTP in vivo at intracerebral concentrations comparable to those that block LTP in vitro. J. Neurosci. 12, 21–34.
Delaney, K.R., Tank, D.W., 1994. A quantitative measurement of the dependence of short-term synaptic enhancement on presynaptic residual calcium. J. Neurosci. 14, 5885–5902.
Delaney, K.R., Zucker, R.S., Tank, D.W., 1989. Calcium in motor nerve terminals associated with posttetanic potentiation. J. Neurosci. 9, 3558–3567.
Derkach, V., Barria, A., Soderling, T.R., 1999. Ca^{2+}/calmodulin-kinase II enhances channel conductance of Œ±-amino-3-hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors. Proc. Natl. Acad. Sci. 96, 3269–3274.
Dineley, K.T., Weeber, E.J., Atkins, C., Adams, J.P., Anderson, A.E., Sweatt, J.D., 2001. Leitmotifs in the biochemistry of LTP induction: amplification, integration and coordination. J. Neurochem. 77, 961–971.
Dittman, J.S., Regehr, W.G., 1997. Mechanism and kinetics of heterosynaptic depression at a cerebellar synapse. J. Neurosci. 17, 9048–9059.

Dittman, J.S., Regehr, W.G., 1998. Calcium dependence and recovery kinetics of presynaptic depression at the climbing fiber to Purkinje cell synapse. J. Neurosci. 18, 6147–6162.
Dobrunz, L.E., Huang, E.P., Stevens, C.F., 1997. Very short-term plasticity in hippocampal synapses. Proc. Natl. Acad. Sci. U.S.A. 94, 14843–14847.
Dobrunz, L.E., Stevens, C.F., 1997. Heterogeneity of release probability, facilitation, and depletion at central synapses. Neuron. 18, 995–1008.
Dolphin, A.C., 2003. G protein modulation of voltage-gated calcium channels. Pharmacol. Rev. 55, 607–627.
Doyere, V., Srebro, B., Laroche, S., 1997. Heterosynaptic LTD and depotentiation in the medial perforant path of the dentate gyrus in the freely moving rat. J. Neurophysiol. 77, 571–578.
Dudek, S.M., Bear, M.F., 1992. Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc. Natl. Acad. Sci. U.S.A. 89, 4363–4367.
Dudel, J., Kuffler, S.W., 1961. Presynaptic inhibition at the crayfish neuromuscular junction. J. Physiol. 155, 543–562.
Eccles, J.C., Schmidt, R.F., Willis, W.D., 1962. Presynaptic inhibition of the spinal monosynaptic reflex pathway. J. Physiol. 161, 282–297.
Emptage, N.J., Reid, C.A., Fine, A., Bliss, T.V., 2003. Optical quantal analysis reveals a presynaptic component of LTP at hippocampal Schaffer-associational synapses. Neuron. 38, 797–804.
Enoki, R., Hu, Y.L., Hamilton, D., Fine, A., 2009. Expression of long-term plasticity at individual synapses in hippocampus is graded, bidirectional, and mainly presynaptic: optical quantal analysis. Neuron. 62, 242–253.
Faas, G.C., Adwanikar, H., Gereau, R.W.T., Saggau, P., 2002. Modulation of presynaptic calcium transients by metabotropic glutamate receptor activation: a differential role in acute depression of synaptic transmission and long-term depression. J. Neurosci. 22, 6885–6890.
Feldman, D.E., 2000. Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex. Neuron. 27, 45–56.
Fioravante, D., Byrne, J.H., 2011. Protein degradation and memory formation. Brain. Res. Bull. 85, 14–20.
Fioravante, D., Liu, R.Y., Byrne, J.H., 2008. The ubiquitin-proteasome system is necessary for long-term synaptic depression in *Aplysia*. J. Neurosci. 28, 10245–10256.
Fioravante, D., Liu, R.Y., Netek, A.K., Cleary, L.J., Byrne, J.H., 2007. Synapsin regulates Basal synaptic strength, synaptic depression, and serotonin-induced facilitation of sensorimotor synapses in *Aplysia*. J. Neurophysiol. 98, 3568–3580.
Fioravante, D., Smolen, P.D., Byrne, J.H., 2006. The 5-HT- and FMRFa-activated signaling pathways interact at the level of the Erk MAPK cascade: potential inhibitory constraints on memory formation. Neurosci. Lett. 396, 235–240.
Fossier, P., Baux, G., Trudeau, L.E., Tauc, L., 1992. Involvement of Ca^{2+} uptake by a reticulum-like store in the control of transmitter release. Neuroscience. 50, 427–434.
Frank, K., Fuortes, M.G., 1957. Presynaptic and postsynaptic inhibition of monosynaptic reflexes. Fed. Proc. 16, 39–40.
Frey, U., Krug, M., Reymann, K.G., Matthies, H., 1988. Anisomycin, an inhibitor of protein synthesis, blocks late phases of LTP phenomena in the hippocampal CA1 region in vitro. Brain. Res. 452, 57–65.
Frey, U., Morris, R.G., 1997. Synaptic tagging and long-term potentiation. Nature. 385, 533–536.
Frey, U., Morris, R.G., 1998. Weak before strong: dissociating synaptic tagging and plasticity-factor accounts of late-LTP. Neuropharmacology. 37, 545–552.
Froemke, R.C., Dan, Y., 2002. Spike-timing-dependent synaptic modification induced by natural spike trains. Nature. 416, 433–438.
Galván, E.J., Calixto, E., Barrionuevo, G.N., 2008. Bidirectional Hebbian plasticity at hippocampal mossy fiber synapses on CA3 interneurons. J. Neurosci. 28, 14042–14055.
Giese, K.P., Fedorov, N.B., Filipkowski, R.K., Silva, A.J., 1998. Autophosphorylation at Thr286 of the alpha calcium-calmodulin kinase II in LTP and learning. Science (New York, N.Y.). 279, 870–873.
Glazewski, S., Chen, C.M., Silva, A., Fox, K., 1996. Requirement for alpha-CaMKII in experience-dependent plasticity of the barrel cortex. Science (New York, N.Y.). 272, 421–423.
Gover, T.D., Jiang, X.Y., Abrams, T.W., 2002. Persistent, exocytosis-independent silencing of release sites underlies homosynaptic depression at sensory synapses in *Aplysia*. J. Neurosci. 22, 1942–1955.
Granger, A.J., Shi, Y., Lu, W., Cerpas, M., Nicoll, R.A., 2013. LTP requires a reserve pool of glutamate receptors independent of subunit type. Nature. 493, 495–500.
Granseth, B., Lagnado, L., 2008. The role of endocytosis in regulating the strength of hippocampal synapses. J. Physiol. 586, 5969–5982.
Grover, L.M., Teyler, T.J., 1990. Two components of long-term potentiation induced by different patterns of afferent activation. Nature. 347, 477–479.
Guan, Z., Giustetto, M., Lomvardas, S., Kim, J.H., Miniaci, M.C., Schwartz, J.H., et al., 2002. Integration of long-term-memory-related synaptic plasticity involves bidirectional regulation of gene expression and chromatin structure. Cell. 111, 483–493.
Guan, Z., Kim, J.H., Lomvardas, S., Holick, K., Xu, S., Kandel, E.R., et al., 2003. p38 MAP kinase mediates both short-term and long-term synaptic depression in *Aplysia*. J. Neurosci. 23, 7317–7325.
Harris, K.M., Fiala, J.C., Ostroff, L., 2003. Structural changes at dendritic spine synapses during long-term potentiation. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 358, 745–748.
Harvey, C.D., Svoboda, K., 2007. Locally dynamic synaptic learning rules in pyramidal neuron dendrites. Nature. 450, 1195–1200.
He, L., Xue, L., Xu, J., Mcneil, B.D., Bai, L., Melicoff, E., et al., 2009. Compound vesicle fusion increases quantal size and potentiates synaptic transmission. Nature. 459, 93–97.
Hebb, D.O., 1949. The Organization of Behavior. Wiley & Sons, New York.
Hegde, A.N., Diantonio, A., 2002. Ubiquitin and the synapse. Nat. Rev. Neurosci. 3, 854–861.
Hegde, A.N., Inokuchi, K., Pei, W., Casadio, A., Ghirardi, M., Chain, D.G., et al., 1997. Ubiquitin C-terminal hydrolase is an immediate-early gene essential for long-term facilitation in *Aplysia*. Cell. 89, 115–126.
Hu, J.Y., Wu, F., Schacher, S., 2006. Two signaling pathways regulate the expression and secretion of a neuropeptide required for long-term facilitation in *Aplysia*. J. Neurosci. 26, 1026–1035.
Huerta, P.T., Lisman, J.E., 1995. Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron. 15, 1053–1063.
Isaacson, J.S., Solis, J.M., Nicoll, R.A., 1993. Local and diffuse synaptic actions of GABA in the hippocampus. Neuron. 10, 165–175.
Ito, M., 1989. Long-term depression. Annu. Rev. Neurosci. 12, 85–102.
Jensen, K., Jensen, M.S., Lambert, J.D., 1999. Role of presynaptic L-type Ca^{2+} channels in GABAergic synaptic transmission in cultured hippocampal neurons. J. Neurophysiol. 81, 1225–1230.
Ji, R.-R., Kohno, T., Moore, K.A., Woolf, C.J., 2003. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends. Neurosci. 26, 696–705.
Jia, M., Nelson, P.G., 1986. Calcium currents and transmitter output in cultured spinal cord and dorsal root ganglion neurons. J. Neurophysiol. 56, 1257–1267.
Junge, H.J., Rhee, J.S., Jahn, O., Varoqueaux, F., Spiess, J., Waxham, M.N., et al., 2004. Calmodulin and Munc13 form a Ca^{2+} sensor/

effector complex that controls short-term synaptic plasticity. Cell. 118, 389–401.
Kamiya, H., Zucker, R.S., 1994. Residual Ca^{2+} and short-term synaptic plasticity. Nature. 371, 603–606.
Kandel, E.R., 2001. The molecular biology of memory storage: a dialogue between genes and synapses. Science. 294, 1030–1038.
Kapur, A., Yeckel, M.F., Gray, R., Johnston, D., 1998. L-Type calcium channels are required for one form of hippocampal mossy fiber LTP. J. Neurophysiol. 79, 2181–2190.
Kassabov, S.R., Choi, Y.B., Karl, K.A., Vishwasrao, H.D., Bailey, C.H., Kandel, E.R., 2013. A single *Aplysia* neurotrophin mediates synaptic facilitation via differentially processed isoforms. Cell Rep. 3, 1213–1227.
Katz, B., Miledi, R., 1968. The role of calcium in neuromuscular facilitation. J. Physiol. 195, 481–492.
Khanbabaie, R., Nesse, W.H., Longtin, A., Maler, L., 2010. Kinetics of fast short-term depression are matched to spike train statistics to reduce noise. J. Neurophysiol. 103, 3337–3348.
Kim, C.-H., Chung, H.J., Lee, H.-K., Huganir, R.L., 2001. Interaction of the AMPA receptor subunit GluR2/3 with PDZ domains regulates hippocampal long-term depression. Proc. Natl. Acad. Sci. 98, 11725–11730.
Klann, E., Sweatt, J.D., 2008. Altered protein synthesis is a trigger for long-term memory formation. Neurobiol. Learn. Mem. 89, 247–259.
Kleinschmidt, A., Bear, M.F., Singer, W., 1987. Blockade of "NMDA" receptors disrupts experience-dependent plasticity of kitten striate cortex. Science (New York, N.Y.). 238, 355–358.
Korogod, N., Lou, X., Schneggenburger, R., 2005. Presynaptic Ca^{2+} requirements and developmental regulation of posttetanic potentiation at the calyx of Held. J. Neurosci. 25, 5127–5137.
Korogod, N., Lou, X., Schneggenburger, R., 2007. Posttetanic potentiation critically depends on an enhanced Ca^{2+} sensitivity of vesicle fusion mediated by presynaptic PKC. Proc. Natl. Acad. Sci. U.S.A. 104, 15923–15928.
Kuromi, H., Kidokoro, Y., 1998. Two distinct pools of synaptic vesicles in single presynaptic boutons in a temperature-sensitive *Drosophila* mutant, shibire. Neuron. 20, 917–925.
Larsen, R.S., Rao, D., Manis, P.B., Philpot, B.D., 2010. STDP in the Developing Sensory Neocortex. Front. Synaptic Neurosci. 2, 9.
Leal, K., Klein, M., 2009. Direct enhancement of presynaptic calcium influx in presynaptic facilitation at *Aplysia* sensorimotor synapses. Mol. Cell. Neurosci. 41, 247–257.
Lee, A.M., Kanter, B.R., Wang, D., Lim, J.P., Zou, M.E., Qiu, C., et al., 2013. Prkcz null mice show normal learning and memory. Nature. 493, 416–419.
Lee, H.-K., Takamiya, K., Han, J.-S., Man, H., Kim, C.-H., Rumbaugh, G., et al., 2003. Phosphorylation of the AMPA receptor GluR1 subunit is required for synaptic plasticity and retention of spatial memory. Cell. 112, 631–643.
Lee, J.S., Kim, M.H., Ho, W.K., Lee, S.H., 2008. Presynaptic release probability and readily releasable pool size are regulated by two independent mechanisms during posttetanic potentiation at the calyx of Held synapse. J. Neurosci. 28, 7945–7953.
Lev-Ram, V., Wong, S.T., Storm, D.R., Tsien, R.Y., 2002. A new form of cerebellar long-term potentiation is postsynaptic and depends on nitric oxide but not cAMP. Proc. Natl. Acad. Sci. U.S.A. 99, 8389–8393.
Levitan, E.S., 2008. Signaling for vesicle mobilization and synaptic plasticity. Mol. Neurobiol. 37, 39–43.
Liao, D., Hessler, N.A., Malinow, R., 1995. Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. Nature. 375, 400–404.
Lin, X.Y., Glanzman, D.L., 1994. Hebbian induction of long-term potentiation of *Aplysia* sensorimotor synapses: partial requirement for activation of an NMDA-related receptor. Proc. Biol. Sci. 255, 215–221.
Lisman, J., 1989. A mechanism for the Hebb and the anti-Hebb processes underlying learning and memory. Proc. Natl. Acad. Sci. U.S.A. 86, 9574–9578.
Lisman, J.E., 1985. A mechanism for memory storage insensitive to molecular turnover: a bistable autophosphorylating kinase. Proc. Natl. Acad. Sci. U.S.A. 82, 3055–3057.
Lisman, J.E., Zhabotinsky, A.M., 2001. A model of synaptic memory: a CaMKII/PP1 switch that potentiates transmission by organizing an AMPA receptor anchoring assembly. Neuron. 31, 191–201.
Liu, R.Y., Cleary, L.J., Byrne, J.H., 2011. The requirement for enhanced CREB1 expression in consolidation of long-term synaptic facilitation and long-term excitability in sensory neurons of *Aplysia*. J. Neurosci. 31, 6871–6879.
Mackey, S.L., Glanzman, D.L., Small, S.A., Dyke, A.M., Kandel, E.R., Hawkins, R.D., 1987. Tail shock produces inhibition as well as sensitization of the siphon-withdrawal reflex of *Aplysia*: possible behavioral role for presynaptic inhibition mediated by the peptide Phe-Met-Arg-Phe-NH2. Proc Natl Acad Sci USA. 84, 8730–8734.
Magleby, K.L., Zengel, J.E., 1982. A quantitative description of stimulation-induced changes in transmitter release at the frog neuromuscular junction. J. Gen. Physiol. 80, 613–638.
Malenka, R.C., Bear, M.F., 2004. LTP and LTD: an embarrassment of riches. Neuron. 44, 5–21.
Malenka, R.C., Kauer, J.A., Perkel, D.J., Mauk, M.D., Kelly, P.T., Nicoll, R.A., et al., 1989. An essential role for postsynaptic calmodulin and protein kinase activity in long-term potentiation. Nature. 340, 554–557.
Malenka, R.C., Lancaster, B., Zucker, R.S., 1992. Temporal limits on the rise in postsynaptic calcium required for the induction of long-term potentiation. Neuron. 9, 121–128.
Malinow, R., Malenka, R.C., 2002. AMPA receptor trafficking and synaptic plasticity. Annu. Rev. Neurosci. 25, 103–126.
Malkinson, G., Spira, M.E., 2013. Release properties of individual presynaptic boutons expressed during homosynaptic depression and heterosynaptic facilitation of the *Aplysia* sensorimotor synapse. Front. Cell. Neurosci. 7, 165.
Mamiya, A., Nadim, F., 2005. Target-specific short-term dynamics are important for the function of synapses in an oscillatory neural network. J. Neurophysiol. 94, 2590–2602.
Markram, H., Lübke, J., Frotscher, M., Sakmann, B., 1997. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science (New York, N.Y.). 275, 213–215.
Markram, H., Tsodyks, M., 1996. Redistribution of synaptic efficacy between neocortical pyramidal neurons. Nature. 382, 807–810.
Martin, K.C., Kosik, K.S., 2002. Synaptic tagging—who's it? Nat. Rev. Neurosci. 3, 813–820.
Martin, S.J., Grimwood, P.D., Morris, R.G., 2000. Synaptic plasticity and memory: an evaluation of the hypothesis. Annu. Rev. Neurosci. 23, 649–711.
Martin, S.J., Morris, R.G.M., 2002. New life in an old idea: the synaptic plasticity and memory hypothesis revisited. Hippocampus. 12, 609–636.
Matsuzaki, M., Honkura, N., Ellis-Davies, G.C., Kasai, H., 2004. Structural basis of long-term potentiation in single dendritic spines. Nature. 429, 761–766.
Matveev, V., Sherman, A., Zucker, R.S., 2002. New and corrected simulations of synaptic facilitation. Biophys. J. 83, 1368–1373.
Mennerick, S., Zorumski, C.F., 1996. Postsynaptic modulation of NMDA synaptic currents in rat hippocampal microcultures by paired-pulse stimulation. J. Physiol. 490, 405–417.
Millar, A.G., Zucker, R.S., Ellis-Davies, G.C., Charlton, M.P., Atwood, H.L., 2005. Calcium sensitivity of neurotransmitter release differs at phasic and tonic synapses. J. Neurosci. 25, 3113–3125.

Miller, P., Zhabotinsky, A.M., Lisman, J.E., Wang, X.J., 2005. The stability of a stochastic CaMKII switch: dependence on the number of enzyme molecules and protein turnover. PLoS Biol. 3, e107.
Miniaci, M.C., Kim, J.H., Puthanveettil, S.V., Si, K., Zhu, H., Kandel, E.R., et al., 2008. Sustained CPEB-dependent local protein synthesis is required to stabilize synaptic growth for persistence of long-term facilitation in *Aplysia*. Neuron. 59, 1024–1036.
Mitchell, S.J., Silver, R.A., 2000a. GABA spillover from single inhibitory axons suppresses low-frequency excitatory transmission at the cerebellar glomerulus. J. Neurosci. 20, 8651–8658.
Mitchell, S.J., Silver, R.A., 2000b. Glutamate spillover suppresses inhibition by activating presynaptic mGluRs. Nature. 404, 498–502.
Miyamoto, E., 2006. Molecular mechanism of neuronal plasticity: induction and maintenance of long-term potentiation in the hippocampus. J. Pharmacol. Sci. 100, 433–442.
Montarolo, P.G., Kandel, E.R., Schacher, S., 1988. Long-term heterosynaptic inhibition in *Aplysia*. Nature. 333, 171–174.
Morgan, S.L., Teyler, T.J., 1999. VDCCs and NMDARs underlie two forms of LTP in CA1 hippocampus in vivo. J. Neurophysiol. 82, 736–740.
Mulkey, R.M., Malenka, R.C., 1992. Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. Neuron. 9, 967–975.
Nabavi, S., Kessels, H.W., Alfonso, S., Aow, J., Fox, R., Malinow, R., 2013. Metabotropic NMDA receptor function is required for NMDA receptor-dependent long-term depression. Proc. Natl. Acad. Sci. U.S.A. 110, 4027–4032.
Neher, E., Sakaba, T., 2008. Multiple roles of calcium ions in the regulation of neurotransmitter release. Neuron. 59, 861–872.
Nevian, T., Sakmann, B., 2006. Spine Ca^{2+} signaling in spike-timing-dependent plasticity. J. Neurosci. 26, 11001–11013.
Ngezahayo, A., Schachner, M., Artola, A., 2000. Synaptic activity modulates the induction of bidirectional synaptic changes in adult mouse hippocampus. J. Neurosci. 20, 2451–2458.
Nicoll, R.A., Malenka, R.C., 1995. Contrasting properties of two forms of long-term potentiation in the hippocampus. Nature. 377, 115–118.
Nicoll, R.A., Oliet, S.H., Malenka, R.C., 1998. NMDA receptor-dependent and metabotropic glutamate receptor-dependent forms of long-term depression coexist in CA1 hippocampal pyramidal cells. Neurobiol. Learn. Mem. 70, 62–72.
Nishiyama, M., Hong, K., Mikoshiba, K., Poo, M.M., Kato, K., 2000. Calcium stores regulate the polarity and input specificity of synaptic modification. Nature. 408, 584–588.
Ogasawara, H., Kawato, M., 2010. The protein kinase Mzeta network as a bistable switch to store neuronal memory. BMC. Syst. Biol. 4, 181.
Ormond, J., Hislop, J., Zhao, Y., Webb, N., Vaillaincourt, F., Dyer, J.R., et al., 2004. ApTrkl, a Trk-like receptor, mediates serotonin-dependent ERK activation and long-term facilitation in *Aplysia* sensory neurons. Neuron. 44, 715–728.
Ostroff, L.E., Fiala, J.C., Allwardt, B., Harris, K.M., 2002. Polyribosomes redistribute from dendritic shafts into spines with enlarged synapses during LTP in developing rat hippocampal slices. Neuron. 35, 535–545.
Otis, T., Zhang, S., Trussell, L.O., 1996. Direct measurement of AMPA receptor desensitization induced by glutamatergic synaptic transmission. J. Neurosci. 16, 7496–7504.
Otmakhov, N., Griffith, L.C., Lisman, J.E., 1997. Postsynaptic inhibitors of calcium/calmodulin-dependent protein kinase type II block induction but not maintenance of pairing-induced long-term potentiation. J. Neurosci. 17, 5357–5365.
Pan, B., Zucker, R.S., 2009. A general model of synaptic transmission and short-term plasticity. Neuron. 62, 539–554.
Pastalkova, E., Serrano, P., Pinkhasova, D., Wallace, E., Fenton, A.A., Sacktor, T.C., 2006. Storage of spatial information by the maintenance mechanism of LTP. Science (New York, N.Y.). 313, 1141–1144.
Patel, S.H., Salvi, J.D., Maoiléidigh, Dáibhid Ó., Hudspeth, A.J., 2012. Frequency-selective exocytosis by ribbon synapses of hair cells in the bullfrog's amphibian papilla. J. Neurosci. 32, 13433–13438.
Pelkey, K.A., McBain, C.J., 2007. Differential regulation at functionally divergent release sites along a common axon. Curr. Opin. Neurobiol. 17, 366–373.
Pfister, J.-P., Dayan, P., Lengyel, M., 2010. Synapses with short-term plasticity are optimal estimators of presynaptic membrane potentials. Nat. Neurosci. 13, 1271–1275.
Pieroni, J.P., Byrne, J.H., 1992. Differential effects of serotonin, FMRFamide, and small cardioactive peptide on multiple, distributed processes modulating sensorimotor synaptic transmission in *Aplysia*. J. Neurosci. 12, 2633–2647.
Piomelli, D., Volterra, A., Dale, N., Siegelbaum, S.A., Kandel, E.R., Schwartz, J.H., et al., 1987. Lipoxygenase metabolites of arachidonic acid as second messengers for presynaptic inhibition of *Aplysia* sensory cells. Nature. 328, 38–43.
Price, G.W., Wilkin, G.P., Turnbull, M.J., Bowery, N.G., 1984. Are baclofen-sensitive GABAB receptors present on primary afferent terminals of the spinal cord?. Nature. 307, 71–74.
Purcell, A.L., Sharma, S.K., Bagnall, M.W., Sutton, M.A., Carew, T.J., 2003. Activation of a tyrosine kinase-MAPK cascade enhances the induction of long-term synaptic facilitation and long-term memory in *Aplysia*. Neuron. 37, 473–484.
Ramoa, A.S., Mower, A.F., Liao, D., Jafri, S.I., 2001. Suppression of cortical NMDA receptor function prevents development of orientation selectivity in the primary visual cortex. J. Neurosci. 21, 4299–4309.
Ren, S.Q., Yan, J.Z., Zhang, X.Y., Bu, Y.F., Pan, W.W., Yao, W., et al., 2013. PKClambda is critical in AMPA receptor phosphorylation and synaptic incorporation during LTP. EMBO. J. 32, 1365–1380.
Rioult-Pedotti, M.S., Friedman, D., Donoghue, J.P., 2000. Learning-induced LTP in neocortex. Science (New York, N.Y.). 290, 533–536.
Roberts, A.C., Glanzman, D.L., 2003. Learning in *Aplysia*: looking at synaptic plasticity from both sides. Trends. Neurosci. 26, 662–670.
Roberts, E.B., Meredith, M.A., Ramoa, A.S., 1998. Suppression of NMDA receptor function using antisense DNA block ocular dominance plasticity while preserving visual responses. J. Neurophysiol. 80, 1021–1032.
Roche, J.P., Packard, M.C., Moeckel-Cole, S., Budnik, V., 2002. Regulation of synaptic plasticity and synaptic vesicle dynamics by the PDZ protein Scribble. J. Neurosci. 22, 6471–6479.
Rochester, N., Holland, J., Haibt, L., Duda, W., 1956. Tests on a cell assembly theory of the action of the brain, using a large digital computer. IRE Trans Inf Theory. 2, 80–93.
Rotman, Z., Deng, P.Y., Klyachko, V.A., 2011. Short-term plasticity optimizes synaptic information transmission. J. Neurosci. 31, 14800–14809.
Royer, S., Coulson, R.L., Klein, M., 2000. Switching off and on of synaptic sites at *Aplysia* sensorimotor synapses. J. Neurosci. 20, 626–638.
Rozov, A., Burnashev, N., Sakmann, B., Neher, E., 2001. Transmitter release modulation by intracellular Ca^{2+} buffers in facilitating and depressing nerve terminals of pyramidal cells in layer 2/3 of the rat neocortex indicates a target cell-specific difference in presynaptic calcium dynamics. J. Physiol. 531, 807–826.
Rudomin, P., Schmidt, R.F., 1999. Presynaptic inhibition in the vertebrate spinal cord revisited. Exp. Brain. Res. 129, 1–37.
Ruiz, A., Fabian-Fine, R., Scott, R., Walker, M.C., Rusakov, D.A., Kullmann, D.M., 2003. GABAA receptors at hippocampal mossy fibers. Neuron. 39, 961–973.
Ruiz, A.J., Kullmann, D.M., 2012. Ionotropic receptors at hippocampal mossy fibers: roles in axonal excitability, synaptic transmission, and plasticity. Front Neural Circuits. 6, 112.

Sacktor, T.C., 2011. How does PKMzeta maintain long-term memory?. Nat. Rev. Neurosci. 12, 9–15.
Sacktor, T.C., Osten, P., Valsamis, H., Jiang, X., Naik, M.U., Sublette, E., 1993. Persistent activation of the zeta isoform of protein kinase C in the maintenance of long-term potentiation. Proc. Natl. Acad. Sci. U.S.A. 90, 8342–8346.
Sakaba, T., Neher, E., 2001. Calmodulin mediates rapid recruitment of fast-releasing synaptic vesicles at a calyx-type synapse. Neuron. 32, 1119–1131.
Sanhueza, M., Mcintyre, C.C., Lisman, J.E., 2007. Reversal of synaptic memory by Ca^{2+}/calmodulin-dependent protein kinase II inhibitor. J. Neurosci. 27, 5190–5199.
Scanziani, M., Salin, P.A., Vogt, K.E., Malenka, R.C., Nicoll, R.A., 1997. Use-dependent increases in glutamate concentration activate presynaptic metabotropic glutamate receptors. Nature. 385, 630–634.
Schacher, S., Montarolo, P.G., 1991. Target-dependent structural changes in sensory neurons of *Aplysia* accompany long-term heterosynaptic inhibition. Neuron. 6, 679–690.
Schneggenburger, R., Meyer, A.C., Neher, E., 1999. Released fraction and total size of a pool of immediately available transmitter quanta at a calyx synapse. Neuron. 23, 399–409.
Sejnowski, T.J., 1977. Statistical constraints on synaptic plasticity. J. Theor. Biol. 69, 385–389.
Sharma, S.K., Carew, T.J., 2004. The roles of MAPK cascades in synaptic plasticity and memory in *Aplysia*: facilitatory effects and inhibitory constraints. Learn. Mem. 11, 373–378.
Sharma, S.K., Sherff, C.M., Stough, S., Hsuan, V., Carew, T.J., 2006. A tropomyosin-related kinase B ligand is required for ERK activation, long-term synaptic facilitation, and long-term memory in *Aplysia*. Proceedings of the National Academy of Sciences of the United States of America. 103, 14206–14210.
Shema, R., Sacktor, T.C., Dudai, Y., 2007. Rapid erasure of long-term memory associations in the cortex by an inhibitor of PKM zeta. Science (New York, N.Y.). 317, 951–953.
Sherrington, C.S., 1906. The Integrative Action of the Nervous System. Yale University Press, New Haven, CT.
Shi, S.-H., Hayashi, Y., Esteban, J.A., Malinow, R., 2001. Subunit-specific rules governing AMPA receptor trafficking to synapses in hippocampal pyramidal neurons. Cell. 105, 331–343.
Shouval, H.Z., Bear, M.F., Cooper, L.N., 2002. A unified model of NMDA receptor-dependent bidirectional synaptic plasticity. Proc. Natl. Acad. Sci. U.S.A. 99, 10831–10836.
Shouval, H.Z., Wang, S.S.H., Wittenberg, G.M., 2010. Spike timing dependent plasticity: a consequence of more fundamental learning rules. Front. Comput. Neurosci.4.
Si, K., Choi, Y.B., White-Grindley, E., Majumdar, A., Kandel, E.R., 2010. *Aplysia* CPEB can form prion-like multimers in sensory neurons that contribute to long-term facilitation. Cell. 140, 421–435.
Si, K., Lindquist, S., Kandel, E.R., 2003. A neuronal isoform of the *Aplysia* CPEB has prion-like properties. Cell. 115, 879–891.
Sippy, T., Cruz-Martin, A., Jeromin, A., Schweizer, F.E., 2003. Acute changes in short-term plasticity at synapses with elevated levels of neuronal calcium sensor-1. Nat. Neurosci. 6, 1031–1038.
Sjöström, P.J., Turrigiano, G.G., Nelson, S.B., 2001. Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. Neuron. 32, 1149–1164.
Sjöström, P.J., Turrigiano, G.G., Nelson, S.B., 2003. Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors. Neuron. 39, 641–654.
Small, S.A., Cohen, T.E., Kandel, E.R., Hawkins, R.D., 1992. Identified FMRFamide-immunoreactive neuron LPL16 in the left pleural ganglion of *Aplysia* produces presynaptic inhibition of siphon sensory neurons. J. Neurosci. 12, 1616–1627.
Smolen, P., Baxter, D.A., Byrne, J.H., 2012. Molecular constraints on synaptic tagging and maintenance of long-term potentiation: a predictive model. PLoS. Comput. Biol. 8, e1002620.
Staubli, U., Lynch, G., 1987. Stable hippocampal long-term potentiation elicited by 'theta' pattern stimulation. Brain. Res. 435, 227–234.
Stent, G.S., 1973. A physiological mechanism for Hebb's postulate of learning. Proc Natl Acad Sci. 70, 997–1001.
Stevens, C.F., Wesseling, J.F., 1998. Activity-dependent modulation of the rate at which synaptic vesicles become available to undergo exocytosis. Neuron. 21, 415–424.
Stevens, C.F., Wesseling, J.F., 1999. Identification of a novel process limiting the rate of synaptic vesicle cycling at hippocampal synapses. Neuron. 24, 1017–1028.
Steward, O., Levy, W.B., 1982. Preferential localization of polyribosomes under the base of dendritic spines in granule cells of the dentate gyrus. J. Neurosci. 2, 284–291.
Sun, H.Y., Dobrunz, L.E., 2006. Presynaptic kainate receptor activation is a novel mechanism for target cell-specific short-term facilitation at Schaffer collateral synapses. J. Neurosci. 26, 10796–10807.
Sun, H.Y., Lyons, S.A., Dobrunz, L.E., 2005. Mechanisms of target-cell specific short-term plasticity at Schaffer collateral synapses onto interneurones versus pyramidal cells in juvenile rats. J. Physiol. 568, 815–840.
Sun, J., Bronk, P., Liu, X., Han, W., Südhof, T.C., 2006. Synapsins regulate use-dependent synaptic plasticity in the calyx of Held by a Ca^{2+}/calmodulin-dependent pathway. Proc. Natl. Acad. Sci. U.S.A. 103, 2880–2885.
Sutton, M.A., Schuman, E.M., 2006. Dendritic protein synthesis, synaptic plasticity, and memory. Cell. 127, 49–58.
Tang, Y., Zucker, R.S., 1997. Mitochondrial involvement in post-tetanic potentiation of synaptic transmission. Neuron. 18, 483–491.
Toonen, R.F., Wierda, K., Sons, M.S., De Wit, H., Cornelisse, L.N., Brussaard, A., et al., 2006. Munc18-1 expression levels control synapse recovery by regulating readily releasable pool size. Proc. Natl. Acad. Sci. U.S.A. 103, 18332–18337.
Towers, S., Princivalle, A., Billinton, A., Edmunds, M., Bettler, B., Urban, L., et al., 2000. GABAB receptor protein and mRNA distribution in rat spinal cord and dorsal root ganglia. Eur. J. Neurosci. 12, 3201–3210.
Valente, P., Casagrande, S., Nieus, T., Verstegen, A.M., Valtorta, F., Benfenati, F., et al., 2012. Site-specific synapsin I phosphorylation participates in the expression of post-tetanic potentiation and its enhancement by BDNF. J. Neurosci. 32, 5868–5879.
Van Der Kloot, W., 1994. Facilitation of transmission at the frog neuromuscular junction at 0°C is not maximal at time zero. J. Neurosci. 14, 5722–5724.
Vickers, E., Kim, M.H., Vigh, J., Von Gersdorff, H., 2012. Paired-pulse plasticity in the strength and latency of light-evoked lateral inhibition to retinal bipolar cell terminals. J. Neurosci. 32, 11688–11699.
Vogt, K.E., Nicoll, R.A., 1999. Glutamate and gamma-aminobutyric acid mediate a heterosynaptic depression at mossy fiber synapses in the hippocampus. Proc. Natl. Acad. Sci. U.S.A. 96, 1118–1122.
Volk, L.J., Bachman, J.L., Johnson, R., Yu, Y., Huganir, R.L., 2013. PKM-zeta is not required for hippocampal synaptic plasticity, learning and memory. Nature. 493, 420–423.
Von Gersdorff, H., Schneggenburger, R., Weis, S., Neher, E., 1997. Presynaptic depression at a calyx synapse: the small contribution of metabotropic glutamate receptors. J. Neurosci. 17, 8137–8146.
Vyshedskiy, A., Lin, J.W., 1997. Activation and detection of facilitation as studied by presynaptic voltage control at the inhibitor of the crayfish opener muscle. J. Neurophysiol. 77, 2300–2315.
Wachtel, H., Kandel, E.R., 1971. Conversion of synaptic excitation to inhibition at a dual chemical synapse. J. Neurophysiol. 34, 56–68.

Walters, E.T., Byrne, J.H., 1985. Long-term enhancement produced by activity-dependent modulation of *Aplysia* sensory neurons. J. Neurosci. 5, 662–672.
Wang, J., Renger, J.J., Griffith, L.C., Greenspan, R.J., Wu, C.F., 1994. Concomitant alterations of physiological and developmental plasticity in Drosophila CaM kinase II-inhibited synapses. Neuron. 13, 1373–1384.
Wang, L.Y., Kaczmarek, L.K., 1998. High-frequency firing helps replenish the readily releasable pool of synaptic vesicles. Nature. 394, 384–388.
Weinberger, N.M., Javid, R., Lepan, B., 1993. Long-term retention of learning-induced receptive-field plasticity in the auditory cortex. Proc. Natl. Acad. Sci. U.S.A. 90, 2394–2398.
Wells, D.G., Dong, X., Quinlan, E.M., Huang, Y.S., Bear, M.F., Richter, J.D., et al., 2001. A role for the cytoplasmic polyadenylation element in NMDA receptor-regulated mRNA translation in neurons. J. Neurosci. 21, 9541–9548.
Whitlock, J.R., Heynen, A.J., Shuler, M.G., Bear, M.F., 2006. Learning induces long-term potentiation in the hippocampus. Science (New York, N.Y.). 313, 1093–1097.
Willis, W.D., 2006. John Eccles' studies of spinal cord presynaptic inhibition. Prog. Neurobiol. 78, 189–214.
Wing, S.S., 2003. Deubiquitinating enzymes--the importance of driving in reverse along the ubiquitin-proteasome pathway. Int. J. Biochem. Cell Biol. 35, 590–605.
Wittenberg, G.M., Wang, S.S.H., 2006. Malleability of spike-timing-dependent plasticity at the CA3-CA1 synapse. J. Neurosci. 26, 6610–6617.
Wojtowicz, J.M., Atwood, H.L., 1988. Presynaptic long-term facilitation at the crayfish neuromuscular junction: voltage-dependent and ion-dependent phases. J. Neurosci. 8, 4667–4674.
Wong, M.Y., Shakiryanova, D., Levitan, E.S., 2009. Presynaptic ryanodine receptor-CamKII signaling is required for activity-dependent capture of transiting vesicles. J. Mol. Neurosci. 37, 146–150.
Woolf, C.J., Salter, M.W., 2000. Neuronal plasticity: increasing the gain in pain. Science (New York, N.Y.). 288, 1765–1769.
Wright, S.N., Brodwick, M.S., Bittner, G.D., 1996. Calcium currents, transmitter release and facilitation of release at voltage-clamped crayfish nerve terminals. J. Physiol. 496, 363–378.
Wu, L.G., Betz, W.J., 1998. Kinetics of synaptic depression and vesicle recycling after tetanic stimulation of frog motor nerve terminals. Biophys. J. 74, 3003–3009.
Wu, L.G., Borst, J.G., 1999. The reduced release probability of releasable vesicles during recovery from short-term synaptic depression. Neuron. 23, 821–832.
Xu, J., He, L., Wu, L.G., 2007. Role of Ca^{2+} channels in short-term synaptic plasticity. Curr. Opin. Neurobiol. 17, 352–359.
Xu, J., Wu, L.G., 2005. The decrease in the presynaptic calcium current is a major cause of short-term depression at a calyx-type synapse. Neuron. 46, 633–645.
Xue, L., Wu, L.G., 2010. Post-tetanic potentiation is caused by two signalling mechanisms affecting quantal size and quantal content. J. Physiol. 588, 4987–4994.
Yamada, W.M., Zucker, R.S., 1992. Time course of transmitter release calculated from simulations of a calcium diffusion model. Biophys. J. 61, 671–682.
Yang, S.N., Tang, Y.G., Zucker, R.S., 1999. Selective induction of LTP and LTD by postsynaptic $[Ca^{2+}]$i elevation. J. Neurophysiol. 81, 781–787.
Yuan, W.X., Chen, S.R., Chen, H., Pan, H.L., 2009. Stimulation of alpha(1)-adrenoceptors reduces glutamatergic synaptic input from primary afferents through GABA(A) receptors and T-type Ca^{2+} channels. Neuroscience. 158, 1616–1624.
Zakharenko, S.S., Zablow, L., Siegelbaum, S.A., 2001. Visualization of changes in presynaptic function during long-term synaptic plasticity. Nat. Neurosci. 4, 711–717.
Zamponi, G.W., Currie, K.P., 2013. Regulation of Ca(V)2 calcium channels by G protein coupled receptors. Biochim. Biophys. Acta. 1828, 1629–1643.
Zengel, J.E., Magleby, K.L., 1980. Differential effects of Ba^{2+}, Sr^{2+}, and Ca^{2+} on stimulation-induced changes in transmitter release at the frog neuromuscular junction. J. Gen. Physiol. 76, 175–211.
Zengel, J.E., Magleby, K.L., 1981. Changes in miniature endplate potential frequency during repetitive nerve stimulation in the presence of Ca^{2+}, Ba^{2+}, and Sr^{2+} at the frog neuromuscular junction. J. Gen. Physiol. 77, 503–529.
Zhang, F., Endo, S., Cleary, L.J., Eskin, A., Byrne, J.H., 1997. Role of transforming growth factor-beta in long-term synaptic facilitation in *Aplysia*. Science. 275, 1318–1320.
Zhang, L.I., Tao, H.W., Holt, C.E., Harris, W.A., Poo, M., 1998. A critical window for cooperation and competition among developing retinotectal synapses. Nature. 395, 37–44.
Zhang, S.J., Jackson, M.B., 1993. GABA-activated chloride channels in secretory nerve endings. Science. 259, 531–534.
Zhang, Y., Smolen, P., Baxter, D.A., Byrne, J.H., 2010. The sensitivity of memory consolidation and reconsolidation to inhibitors of protein synthesis and kinases: computational analysis. Learn. Mem. 17, 428–439.
Zhao, Y., Klein, M., 2002. Modulation of the readily releasable pool of transmitter and of excitation-secretion coupling by activity and by serotonin at *Aplysia* sensorimotor synapses in culture. J. Neurosci. 22, 10671–10679.
Zhong, N., Beaumont, V., Zucker, R.S., 2001. Roles for mitochondrial and reverse mode Na^{+}/Ca^{2+} exchange and the plasmalemma Ca^{2+} ATPase in post-tetanic potentiation at crayfish neuromuscular junctions. J. Neurosci. 21, 9598–9607.
Zhong, Y., Wu, C.F., 1991. Altered synaptic plasticity in *Drosophila* memory mutants with a defective cyclic AMP cascade. Science. 251, 198–201.
Zucker, R.S., 1989. Short-term synaptic plasticity. Annu. Rev. Neurosci. 12, 13–31.
Zucker, R.S., 1994. Calcium and short-term synaptic plasticity. Neth. J. Zool. 44, 495–512.
Zucker, R.S., Regehr, W.G., 2002. Short-term synaptic plasticity. Annu. Rev. Physiol. 64, 355–405.