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Presynaptic LTP and LTD of Excitatory and Inhibitory Synapses

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Ubiquitous forms of long-term potentiation (LTP) and depression (LTD) are caused by enduring increases or decreases in neurotransmitter release. Such forms of presynaptic plasticity are equally observed at excitatory and inhibitory synapses and the list of locations expressing presynaptic LTP and LTD continues to grow. In addition to the mechanistically distinct forms of postsynaptic plasticity, presynaptic plasticity offers a powerful means to modify neural circuits. A wide range of induction mechanisms has been identified, some of which occur entirely in the presynaptic terminal, whereas others require retrograde signaling from the postsynaptic to presynaptic terminals. In spite of this diversity of induction mechanisms, some common induction rules can be identified across synapses. Although the precise molecular mechanism underlying long-term changes in transmitter release in most cases remains unclear, increasing evidence indicates that presynaptic LTP and LTD can occur *in vivo* and likely mediate some forms of learning.

At several excitatory and inhibitory synapses, neuronal activity can trigger enduring increases or decreases in neurotransmitter release, thereby producing long-term potentiation (LTP) or long-term depression (LTD) of synaptic strength, respectively. In the last decade, many studies have revealed that these forms of plasticity are ubiquitously expressed in the mammalian brain, and accumulating evidence indicates that they may underlie behavioral adaptations occurring *in vivo*. These studies have also uncovered a wide range of induction mechanisms, which converge on the presynaptic terminal where an enduring modification in the neurotransmitter release process takes place. Interestingly, presynaptic forms of LTP/LTD can coexist with classical forms of post-

synaptic plasticity. Such diversity expands the dynamic range and repertoire by which neurons modify their synaptic connections. This review discusses mechanistic aspects of presynaptic LTP and LTD at both excitatory and inhibitory synapses in the mammalian brain, with an emphasis on recent findings.

INDUCTION MECHANISMS

As illustrated in Figure 1, presynaptic LTP/LTD at both excitatory and inhibitory synapses can be induced in a homosynaptic or heterosynaptic manner, with induction occurring either entirely at the presynaptic terminal or requiring a retrograde messenger arising from the postsynaptic neuron. Each of these four induction

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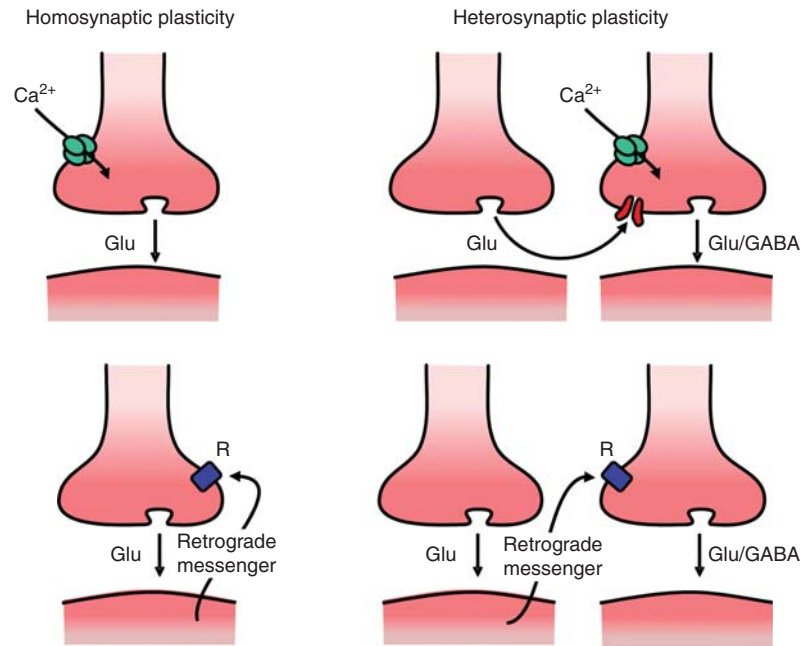


Figure 1. Four basic arrangements for presynaptic LTP and LTD. (*Top row*) Illustrates examples where plasticity is entirely induced presynaptically, either in a homosynaptically (e.g., mossy fiber LTP) or heterosynaptically (e.g., associative cortico-lateral amygdala LTP of glutamatergic transmission). (*Bottom row*) Examples requiring retrograde signaling generated either at the same synapse receiving the signal (*left*, e.g., eCB-LTD at excitatory synapses) or at a neighboring synapse (*right*, e.g., eCB-LTD at inhibitory synapses).

mechanisms will be discussed and is summarized in Table 1.

Mossy Fiber to CA3 Pyramidal Cell Synapse as a Model for Presynaptic LTP/LTD

Arguably, the best characterized form of presynaptic LTP can be found at the mossy fiber (MF) synapse between dentate gyrus granule cells and hippocampal CA3 pyramidal (Nicoll and Schmitz 2005). MF-LTP is a prototype for mechanistically similar, presynaptically expressed, NMDAR-independent and cAMP/PKA-dependent forms of LTP found in several brain areas including the cerebellum (Salin et al. 1996a), thalamus (Castro-Alamancos and Calcagnotto 1999), subiculum (Behr et al. 2009), amygdala (Lopez de Armentia and Sah 2007), and neocortex (Chen et al. 2009). MF-LTP is mechanistically distinct from classical NMDAR-dependent LTP at the Schaffer collat-

eral to CA1 pyramidal cell synapse (Sch-CA1) (Nicoll and Malenka 1995). Repetitive activation of MFs with high frequency stimulation (HFS, typically 100 Hz bursts), or naturally occurring activity patterns (Gundlfinger et al. 2010; Mistry et al. 2010), triggers a long-lasting increase in presynaptic release probability (Pr) and a potentiation of the excitatory synaptic response (Nicoll and Schmitz 2005).

Strong evidence indicates MF-LTP results from enhanced glutamate release, including changes in paired-pulse facilitation, failure rate, coefficient of variation, miniature EPSC activity, and MK-801 sensitivity (Nicoll and Schmitz 2005). Unlike Sch-CA1 LTP induction, classical presynaptic MF-LTP is NMDAR-independent (Harris and Cotman 1986). Evidence indicates that LTP is induced by an activity-dependent increase in Ca^{2+} concentration within MF terminals (Zalutsky and Nicoll 1990; Mellor and Nicoll 2001) (but see Yeckel et al. 1999). Although

**Table 1.** Presynaptic long-term plasticity at excitatory and inhibitory synapses in the mammalian brain

Brain area (species)	LTP/LTD	Synapse type	Induction protocol ^a	Induction requirements	References ^b
Visual cortex (rat)	LTD	Excitatory inputs, L5 pyramidal cell pairs	STDP pairing protocol	eCB signaling; postsynaptic Ca ²⁺ ; presynaptic NMDAR	Sjöstrom et al. 2003; Corlew et al. 2007
Immature visual cortex (mouse)	LTD	Excitatory inputs L4 to L2/3 neurons	TBS	eCB signaling; mGluR5	Huang et al. 2008
Visual cortex (mouse, rat)	LTD	GABAergic inputs to L2/3 neurons	TBS	eCB signaling; mGluR5	Jiang et al. 2010
Visual cortex (mouse)	LTP	Excitatory inputs on fast spiking GABAergic interneurons		mGluR5 (but not mGluR1), postsynaptic calcium, NMDAR-independent	Sarihi et al. 2008
Somatosensory (barrel) cortex (rat)	LTD	Excitatory inputs to L2/3 neurons	STDP pairing protocol	eCB signaling, group I mGluR; postsynaptic Ca ²⁺ ; presynaptic NMDAR	Bender et al. 2006; Nevian and Sakmann 2006
Sensory-motor cortex (mouse)	LTP	Excitatory inputs on somatostatin-expressing interneurons	TBS	NMDAR-independent, postsynaptic calcium-independent, PKA dependent	Chen et al. 2009
Somatosensory cortex (rat)	LTP	Pyramidal cell on LTS GABAergic interneurons	STDP pairing protocol	NMDAR-dependent	Lu et al. 2007
Somatosensory cortex (rat)	LTD	Pyramidal cell on LTS GABAergic interneurons	STDP pairing protocol	mGluR-dependent, NMDAR/CB1R-independent	Lu et al. 2007
Prefrontal cortex (mouse)	LTD	Excitatory inputs L2/3 to L5/6 neurons	Moderate 10 Hz stimulation for 10 min	eCB signaling; postsynaptic Ca ²⁺ ; mGluR5	Lafourcade et al. 2007
Prefrontal cortex (rat, mouse)	LTD	GABAergic inputs to L5/6 neurons	Moderate 5 Hz stimulation for 5–10 min	eCB signaling; group I mGluR; presynaptic D2R	Chiu et al. 2010
Thalamus (mouse)	LTP	Cortical inputs to ventrobasal neurons	(100 stim, 10 Hz) × 6	NMDAR-independent	Castro-Alamancos and Calcagnotto 1999
Hippocampus (mouse, rat, guinea pig)	LTP	Mossy fiber to CA3 pyramidal cell	HFS (25–100 Hz)	cAMP/PKA, R-type VGCC, NMDAR-independent	Harris and Cotman 1986; Zalutsky and Nicoll 1990; Huang et al. 1994; Weisskopf et al. 1994; Xiang et al. 1994; Yeckel et al. 1999 (see text for additional references)

Continued

Presynaptic Long-Term Plasticity



Table 1. Continued

Brain area (species)	LTP/LTD	Synapse type	Induction protocol ^a	Induction requirements	References ^b
Dentate (rat)	LTP	Mossy fiber to dentate gyrus basket cell	30 Hz bursts paired with postsynaptic action potentials	PKC-dependent, PKA-independent, postsynaptic calcium	Alle et al. 2001
Dentate (rat)	LTP	Mossy fiber to mossy cells	HFS (100 Hz)	NMDAR-independent	Lysetskiy et al. 2005
Hippocampus (mouse, rat)	LTD	Mossy fiber to <i>s.lucidum</i> interneurons	HFS (100 Hz)	Postsynaptic Ca ²⁺ via CP-AMPA, presynaptic mGluR7, PKC	Maccaferri et al. 1998; Lei and McBain 2004; Pelkey et al. 2005, 2006
Hippocampus (rat)	LTP	Mossy fiber to CA3 <i>s.lacunosum moleculare</i> interneurons	HFS (100 Hz)	Postsynaptic Ca ²⁺ , L-type VGCC, NMDAR-independent, postsynaptic PKA	Galvan et al. 2008, 2010
Hippocampus (neonatal rat)	LTP	Immature mossy fiber to CA3 pyramidal cell	STDP pairing protocol	Postsynaptic Ca ²⁺ ; L-type VGCC; NMDAR-independent; BDNF/trkB; postsynaptic cAMP/PKA	Sivakumaran et al. 2009
Hippocampus (rat)	LTP	Excitatory inputs on CA1 interneurons	HFS (100 Hz), TBS	Postsynaptic Ca ²⁺ via CP-AMPA, NMDAR-independent	Lamsa et al. 2007; Oren et al. 2009; Nissen et al. 2010
Hippocampus (rat)	LTP	Excitatory inputs on CA1 interneurons	TBS paired with postsynaptic depolarization	Postsynaptic Ca ²⁺ and mGluR1 activation	Perez et al. 2001; Lapointe et al. 2004; Topolnik et al. 2006
Hippocampus	LTD	Excitatory inputs on CA1 interneurons	HFS (100 Hz)	Retrograde signaling by 12-(S)-HPETE, presynaptic TRPV1, group I mGluR, NMDAR-independent	Gibson et al. 2008
Subiculum (mouse, rat)	LTP	CA1-subiculum pyramidal cell	HFS (100 Hz)	cAMP/PKA, postsynaptic Ca ²⁺ -independent	Kokaia 2000; Wozny et al. 2008a,b
Hippocampus (mouse)	LTP	Schaffer collateral-CA1 pyramidal cell	HFS (200 Hz)	Postsynaptic Ca ²⁺ , L-type VGCC	Zakharenko et al. 2001; Bayazitov et al. 2007
Hippocampus (mouse)	LTP	Perforant path-CA1 pyramidal cells	HFS (200 Hz)	Postsynaptic NMDARs; L-type, T-type VGCCs	Ahmed and Siegelbaum 2009



Hippocampus (rat, mouse)	LTD	Inhibitory inputs to CA1 pyramidal cells	HFS, TBS	eCB signaling; group I mGluRs; cAMP/PKA; postsynaptic Ca ²⁺ and NMDAR-independent	Chevaleyre and Castillo 2003, 2002
Cerebellum (mouse, rat, guinea pig)	LTP	Parallel fiber to Purkinje cell	4–10 Hz stimulation (e.g., 8 Hz, 30 Hz)	cAMP/PKA; NMDAR and postsynaptic Ca ²⁺ -independent	Sakurai 1987; Shibuki and Okada 1992; Salin et al. 1996b; Storm et al. 1998; Linden and Ahn 1999; Bender et al. 2009
Cerebellum (mouse)	LTD	Parallel fiber to Purkinje cell	4 Hz, in the presence of PKA inhibitor	eCB signaling NMDAR	Qiu and Knopfel 2009
Cerebellum (rat)	LTP	Parallel fiber to molecular layer interneuron	8 Hz stimulation for 30 s	cAMP/PKA	Bender et al. 2009; Rancillac and Crepel 2004
Cerebellum (rat)	LTP	Parallel fiber to stellate cell	Pairing protocol: 2 Hz for 60 s, postsynaptic depolarization	cAMP-independent, NO-dependent	Rancillac and Crepel 2004
Cerebellum (rat)	LTD	Parallel fiber to stellate cell	4 × 25 stim at 30 Hz	Postsynaptic Ca ²⁺ , CP-AMPA, mGluR1, eCB retrograde signaling, NMDAR-independent	Soler-Llavina and Sabatini 2006
Cerebellum (mouse)	LTP	Stellate cell-stellate cell	HFS (100 Hz) of parallel fibers	Presynaptic NMDARs	Liu and Lachamp 2006; Lachamp et al. 2009
Lateral amygdala (rat, mouse)	LTP	Cortico-lateral amygdala neurons	Simultaneous repetitive stimulation (Poisson train, 30 Hz average) of thalamic and cortical afferents	Presynaptic NMDAR, cAMP/PKA	Humeau et al. 2003; Fourcaudot et al. 2008, 2009
Lateral amygdala (rat)	LTP	Cortico-lateral amygdala neurons	Pairing protocol (80 stim, 2 Hz) +30 mV postsynaptic depolarization	Postsynaptic Ca ²⁺ , NMDAR, L-type VGCC	Tsvetkov et al. 2002
Lateral amygdala (rat)	LTP	Thalamic-lateral amygdala neurons	HFS (100 Hz)	Postsynaptic Ca ²⁺ , presynaptic cAMP/PKA	Huang and Kandel 1998
Lateral amygdala (rat)	LTP	Thalamic-lateral amygdala neurons	PP stimulation (50 ms ISI), 2 Hz for 2 min	Presynaptic Ca ²⁺ , GluK1-containing KAR, NMDAR-independent	Shin et al. 2010

Continued

Presynaptic Long-Term Plasticity



Table 1. Continued

Brain area (species)	LTP/LTD	Synapse type	Induction protocol ^a	Induction requirements	References ^b
Central amygdala (guinea pig)	LTP	Thalamic-central amygdala neurons	HFS (100 Hz) paired with brief suprathreshold depolarization	Presynaptic NMDAR	Samson and Pare 2005
Central amygdala (rat)	LTP	Nociceptive inputs to central amygdala neurons	HFS (100 Hz)	cAMP/PKA; NMDAR-independent	Lopez de Armentia and Sah 2007
Lateral amygdala (mouse)	LTD	GABAergic inputs to lateral amygdala	LFS (1 Hz)	eCB signaling; mGluR1; postsynaptic PKA activity	Marsicano et al. 2002; Azad et al. 2004
Dorsal striatum (rat, mouse)	LTD	Glutamatergic cortical inputs to medium spiny neurons	HFS (100 Hz), STDP pairing protocol	eCB signaling; group I mGluR; postsynaptic Ca ²⁺	Gerdeman et al. 2002; Kreitzer and Malenka 2007; Shen et al. 2008
Nucleus accumbens (mouse)	LTD	Glutamatergic cortical afferents to nucleus accumbens	Moderate 13 Hz stimulation for 10 min	eCB signaling; mGluR5; postsynaptic Ca ²⁺	Robbe et al. 2002b
Nucleus accumbens (mouse)	LTD	Cortical afferents to nucleus accumbens	HFS (100 Hz)	mGluR2/3, cAMP/PKA signaling	Robbe et al. 2002a
Ventral tegmental area (rat)	LTD	GABAergic inputs to dopamine neurons	Moderate 10 Hz stimulation for 5 min	eCB signaling; group I mGluR, D2R	Pan et al. 2008
Ventral tegmental area (rat)	LTP	GABAergic inputs to dopamine neurons	HFS (100 Hz)	Postsynaptic Ca ²⁺ ; NMDAR; Nitric Oxide/cGMP signaling	Nugent et al. 2007
Dorsal Cochlear Nucleus (mouse)	LTD	Glutamatergic inputs to Carthwheel GABAergic interneuron	STDP pairing protocol	eCB signaling; group I mGluR-independent	Tzounopoulos et al. 2007

^aMost typical induction protocol is indicated. Only examples of synaptically induced (i.e., no chemically induced) LTP/LTD in brain tissue are listed.

^bBecause of space limitations, not all references are listed (see text).

Abbreviations: HFS, high frequency stimulation; TBS, theta-burst stimulation; PPF, paired-pulse facilitation; CV, coefficient of variation; STDP, spike timing-dependent plasticity; VGCC, voltage-gated calcium channel, eCB, endocannabinoid; CP, Ca²⁺-permeable; D2R, type 2 dopamine receptor; n/a, not available.



glutamate release at MF-CA3 synapses is mediated by N- and P/Q-type voltage gated Ca^{2+} channels (VGCCs), MF-LTP can occur with both of these channel types blocked (Castillo et al. 1994). In contrast, R-type channels contribute significantly to MF-LTP, despite playing a minor role in overall presynaptic Ca^{2+} influx and basal transmission (Breustedt et al. 2003; Dietrich et al. 2003). Ca^{2+} influx via R-type VGCCs appears to preferentially access presynaptic signals that trigger MF-LTP, as recently suggested for parallel fiber LTP (Myoga and Regehr 2011). Pharmacological manipulations and genetic analyses using knockout mice indicates that presynaptic Ca^{2+} activates a Ca^{2+} /calmodulin-dependent adenylyl cyclase, leading to enhanced presynaptic cAMP levels and activation of PKA, which is necessary for MF-LTP (Huang et al. 1994; Weisskopf et al. 1994; Villacres et al. 1998; Wang et al. 2003). PKA then phosphorylates presynaptic substrate(s) to cause a long-lasting increase in transmitter release (see below).

An alternative mechanism for MF-LTP induction has been proposed. The leading event is a postsynaptic Ca^{2+} enhancement via L-type VGCCs and group I mGluR-stimulated release of Ca^{2+} from internal stores. Ca^{2+} mobilizes a retrograde signal in a PKA-dependent manner (Jaffe and Johnston 1990; Kapur et al. 1998; Yeckel et al. 1999). A similar mechanism has recently been reported at some MF to CA3 interneuron synapses (Galvan et al. 2008, 2010). This induction model is consistent with Hebbian MF-LTP (Urban and Barrionuevo 1996) whereby plasticity is triggered by both presynaptic activity that releases glutamate to activate postsynaptic group I mGluRs, and postsynaptic depolarization to activate L-type VGCCs. Numerous studies have not been able to confirm a postsynaptic model of classical MF-LTP induction (for a review, see Nicoll and Schmitz 2005), and as a result, no agreement has yet emerged. Interestingly, at immature MF-CA3 synapses, which mainly release GABA that acts as excitatory neurotransmitter at early developmental stages, correlated presynaptic and postsynaptic activity triggers presynaptically expressed LTP, whose induction requires postsynaptic Ca^{2+} rise and postsynaptic cAMP/PKA signaling

(Sivakumaran et al. 2009). Given that brain-derived neurotrophic factor (BDNF)/tyrosine kinase B (trkB) signaling is also required, BDNF could act as a retrograde messenger (see below), a possibility that needs to be directly tested. Another mechanism of induction requiring retrograde signaling has been proposed at mature MF-CA3 synapses. The model involves transsynaptic interaction between postsynaptic EphB receptor tyrosine kinases and presynaptic B-Ephrin ligands resulting, via an unknown mechanism, in a long-lasting increase in transmitter release (Contractor et al. 2002; Armstrong et al. 2006).

MF synapses also express presynaptic LTD. Similar protocols of stimulation commonly used to trigger NMDAR-dependent LTD at SchCA1 synapses also induce a MF-CA3 homosynaptic LTD expressed as a reduction in glutamate release (Kobayashi et al. 1996). The MF-CA3 synapse is one of few locations where bidirectional presynaptic LTP/LTD can be observed in the central nervous system. Presynaptic MF-LTD induction is NMDAR-independent and seems to require presynaptic mGluR2 as indicated by studies using nonselective mGluR antagonists and mGluR2 knockout mice (Yokoi et al. 1996; Tzounopoulos et al. 1998; Kobayashi et al. 1999). Intriguingly, none of these manipulations fully abolishes MF-LTD. Exogenous mGluR2 activation is not sufficient for induction and must be associated with MF activity, which presumably provides a Ca^{2+} -dependent signal (Tzounopoulos et al. 1998; Kobayashi et al. 1999). Given that $\text{G}_{i/o}$ coupled mGluR2 activation leads to decreased cAMP/PKA activity, MF-LTD could be a reversal of the presynaptic process involved in MF-LTP. Unexpectedly, two recent studies have called into question the induction mechanism underlying MF-LTD. Using more specific and potent group II mGluRs antagonists, as well as mGluR2/3 double knockout mice, these studies still observed presynaptic MF-LTD (Wostrack and Dietrich 2009; Lyon et al. 2011). MF-LTD induced in mGluR2/3 double knockout mice was abolished by pharmacologically blocking kainate receptors (Lyon et al. 2011), raising the intriguing possibility that these receptors, via a metabotropic action,

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could be involved in the induction of presynaptic MF-LTD (Negrete-Diaz et al. 2007). Further studies are required to determine the precise mechanism of presynaptic MF-LTD.

Other presynaptic forms of plasticity that are mechanistically similar to MF-LTP have been identified in multiple brain areas, including the cerebellum, the amygdala (see Pape and Pare 2010) and subiculum (Table 1) (see Behr et al. 2009). In the cerebellum, repetitive parallel fiber (PF) stimulation triggers presynaptic LTP at PF to Purkinje cell synapses. Induction does not require postsynaptic glutamate receptor activation or Ca^{2+} rises but, as for MF-LTP, requires cAMP/PKA signaling (Sakurai 1987; Shibuki and Okada 1992; Salin et al. 1996b; Storm et al. 1998; Linden and Ahn 1999; Bender et al. 2009). Similar presynaptic LTP was subsequently observed at PF to molecular layer interneuron synapses (Rancillac and Crepel 2004; Bender et al. 2009). Like MF synapses, PF synapses display bidirectional presynaptic plasticity. Indeed, PF inputs onto both Purkinje cells (Qiu and Knopfel 2009) and molecular layer interneurons (Soler-Llavina and Sabatini 2006) can undergo presynaptic LTD. However, unlike at MF synapses, presynaptic LTD at PF synapses seems to be mediated by endocannabinoids (see below).

Presynaptic LTP/LTD at Excitatory Synapses onto Interneurons

In addition to CA3 pyramidal cells, MFs establish synapses with multiple classes of interneurons, such as excitatory mossy cells in the hilus, and inhibitory interneurons in both CA3 and dentate gyrus. Although HFS of MFs triggers a presynaptic form of LTP in mossy cells that is reportedly identical to classical MF-LTP in CA3 pyramidal cells (Lysetskiy et al. 2005), a slightly modified stimulation paradigm applied to presynaptic dentate granule cells triggers a form of presynaptic LTP at MF–dentate gyrus basket cells whose induction requires a rise in postsynaptic Ca^{2+} . Because this LTP is expressed presynaptically, a retrograde messenger is required (Alle et al. 2001) but the identity of this messenger remains unknown. Intriguingly, unlike

classical MF-LTP in principal neurons, LTP at MF-basket cell synapses requires PKC but not PKA activity (Alle et al. 2001).

Whereas repetitive stimulation triggers presynaptic LTP at both MF-mossy cell and MF-basket cell synapses, a very different picture emerges at MF-interneuron synapses (mainly MF to *s. lucidum* interneurons, a.k.a. MF-SLIN synapses) (for a review, see McBain 2008). Remarkably, the same stimulation paradigm that induces presynaptic LTP in both principal neurons and mossy cells triggers a NMDAR-independent form of presynaptic LTD at some MF-interneuron synapses (Maccaferri et al. 1998). These synapses were subsequently identified as those expressing Ca^{2+} -permeable (CP), GluR2-lacking AMPARs (Toth et al. 2000; Lei and McBain 2004). Induction of this form of LTD requires a postsynaptic Ca^{2+} rise via CP-AMPA receptors, and activation of presynaptic mGluR7 receptors, which triggers PKC and a down-regulation of Ca^{2+} influx through P/Q-type VGCCs to reduce probability of release (Pelkey et al. 2005, 2006). Activation of mGluR7 is necessary but not sufficient to induce LTD; postsynaptic activity and the associated postsynaptic Ca^{2+} rise are also required to presumably promote the mobilization of an as yet unidentified retrograde messenger.

Unexpectedly, mGluR7 not only mediates a long-lasting reduction in glutamate release but also acts as a metaplastic switch such that on binding of agonist, mGluR7 is rapidly internalized and delivery of subsequent HFS then triggers a de-depression or LTP of synaptic transmission (Pelkey et al. 2005). It therefore appears that the presence or absence of mGluR7 on the presynaptic surface dictates whether the MF-SLIN synapse weakens or strengthens in response to HFS. The de-depression/LTP unmasked by mGluR7 internalization is caused by an enhancement in glutamate release, the molecular basis of which will be discussed below. Repetitive activation of MFs can also trigger presynaptic LTP on CA3 lacunosum-moleculare interneurons (Galvan et al. 2011). How exactly these multiple forms of synaptic plasticity of MFs on interneurons regulate the CA3 network excitability remains to be determined.

Several other examples of presynaptic LTP/LTD have been identified at glutamatergic inputs onto interneurons throughout the brain (Table 1) (for recent, comprehensive reviews see McBain and Kauer 2009; Kullmann and Lamsa 2011). As for the examples discussed above, induction typically requires postsynaptic Ca^{2+} to rise in an NMDAR-independent manner. A common source includes Ca^{2+} influx via CP-AMPA receptors, although L-type VGCCs and group I mGluR-stimulated release of Ca^{2+} from internal stores may also contribute. What determines the sign of plasticity (i.e., LTP or LTD) at a given synapse is unclear but both postsynaptic and presynaptic factors may contribute.

Presynaptic NMDAR-Dependent Plasticity

Increasing evidence supports the notion that presynaptic NMDARs (preNMDARs) can regulate transmitter release and play a key role in the induction of presynaptic forms of plasticity (Duguid and Sjöström 2006; Corlew et al. 2008; Rodríguez-Moreno et al. 2010). Physiological studies strongly suggest that preNMDARs can enhance both spontaneous and evoked transmitter release (glutamate and GABA) at some synapses, and there is anatomical evidence supporting a presynaptic localization (Corlew et al. 2008). A key experiment in support of preNMDAR-dependent forms of plasticity is the demonstration that global antagonism of NMDAR blocks induction, whereas blocking postsynaptic NMDARs (e.g., by loading cells with the NMDAR channel blocker MK-801) has no effect. Like other presynaptic ionotropic receptors (Engelman and MacDermott 2004), preNMDARs facilitate transmitter release most likely by direct depolarization of the presynaptic terminal, by permeating Ca^{2+} , or both. An alternative mechanism not requiring membrane depolarization and Ca^{2+} influx cannot be discarded. Endogenous glutamate that activates preNMDARs can arise from the same terminal (acting as an autoreceptor) or neighboring terminals (acting as a heteroreceptor), although postsynaptic dendritic release (Duguid and Smart 2004) and release from glia could also contribute (Parpura and Zorec 2010).

In neocortex (visual and somatosensory cortices, see Table 1), there is strong evidence (Sjöström et al. 2003; Bender et al. 2006; Nevian and Sakmann 2006; Corlew et al. 2007; Rodríguez-Moreno and Paulsen 2008) that preNMDARs play a key role in the induction of the LTD component of spike timing-dependent plasticity (STDP), an associative form of plasticity in which the precise temporal relationship between presynaptic and postsynaptic activity determines the direction (t-LTP or t-LTD) and the magnitude of the resulting change in synaptic strength (for a recent review, see Caporale and Dan 2008). Induction of preNMDAR-dependent t-LTD requires postsynaptic Ca^{2+} rise and activation of group I mGluRs (at least in somatosensory cortex). In addition, this t-LTD is expressed presynaptically as a long-lasting reduction in transmitter release, implicating a retrograde signal, which has been identified as an endogenous cannabinoid (Sjöström et al. 2003; Bender et al. 2006; Nevian and Sakmann 2006). As discussed below, endocannabinoids (eCB) are well-established retrograde messengers mediating most known forms of presynaptic LTD in the brain (Heifets and Castillo 2009). Because eCBs mediate their effects by targeting presynaptic cannabinoid receptors, an obvious question is how these receptors interact with NMDARs at the presynaptic terminal to induce t-LTD. PreNMDARs could have an instructive or regulatory role in t-LTD. In the first case, given the dual requirement of depolarization and glutamate binding for NMDAR gating, preNMDARs act as coincidence detectors of presynaptic action potential-mediated depolarization and glutamate release. As expected, t-LTD only occurs if these receptors are activated within a narrow interval, although presynaptic cannabinoid receptors may also contribute to set this time window for t-LTD (Sjöström et al. 2003; Duguid and Sjöström 2006). In a regulatory role, preNMDARs somehow facilitate induction but the coincidence detection occurs postsynaptically as a result of group I mGluR activation by glutamate and postsynaptic Ca^{2+} rise via L-type VGCCs (Bender et al. 2006; Nevian and Sakmann 2006). In this case, mGluRs and Ca^{2+} would act synergistically to

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mobilize eCBs as shown in other systems (Hashimoto et al. 2007). These examples in neocortex, suggest that the precise interaction of preNMDARs and eCB signaling in setting the characteristic time window for t-LTD induction is synapse-specific. It will be interesting to know the generality of preNMDAR-dependent t-LTD in other brain areas especially because preNMDARs expression and subunit composition can be developmentally regulated (Corlew et al. 2008; Larsen et al. 2011).

Several studies have shown that activation of preNMDARs mediates other forms of presynaptic LTP/LTD at both excitatory and inhibitory synapses. Two forms of preNMDAR-dependent LTP, both expressed presynaptically, have been reported in the amygdala. In the lateral amygdala (LA), repeated coincident stimulation of converging cortical and thalamic excitatory afferents on LA projection neurons induces associative LTP at cortical but not thalamic inputs (Humeau et al. 2003). In addition, induction is independent of postsynaptic activity, including depolarization, Ca^{2+} rise and activation of postsynaptic NMDARs, but requires cAMP/PKA signaling (Fourcaudot et al. 2008). A potential mechanism for this heterosynaptic associative form of plasticity is that glutamate released by thalamic afferents might directly activate preNMDARs on cortical presynaptic terminals (adding to the homosynaptic activation by glutamate released from these terminals), thereby promoting presynaptic Ca^{2+} increase, which, like for other forms of presynaptic LTP (e.g., MF-LTP), triggers a long-lasting cAMP/PKA-dependent increase in transmitter release. The other form of preNMDAR-dependent LTP in amygdala has been reported at thalamic afferents on medial sector neurons in the central nucleus (Samson and Pare 2005). Unlike cortical-LA LTP, LTP in central amygdala is homosynaptic and nonassociative, and much less is known about its molecular mechanism of induction.

PreNMDAR-dependent LTP and LTD have also been reported at GABAergic synapses (Lien et al. 2006; Liu et al. 2007). In rodent cerebellar cortex, glutamate released from parallel fibers induces a long-lasting increase of GABA release

from stellate cells, presumably by activating preNMDARs on their terminals (Liu and Lachamp 2006). This heterosynaptic form of LTP also requires cAMP/PKA signaling (Lachamp et al. 2009). Finally, in the developing *Xenopus* retinotectal system, light stimuli or theta burst stimulation of the optic nerve triggers presynaptic LTD of GABAergic synaptic transmission on tectal neurons (Lien et al. 2006). Activation of preNMDARs is necessary but not sufficient for induction. Coincident interneuron activity is also required, and such activity presumably provides the required depolarization for preNMDAR gating as well as Ca^{2+} influx through presynaptic VGCCs that may also contribute to the inhibitory LTD at hippocampal synapses (Heifets et al. 2008). It remains to be seen whether this type of heterosynaptic LTD of GABAergic transmission also occurs in the mammalian brain.

Retrograde Signaling and Presynaptic LTD/LTP

Presynaptic forms of plasticity that include a postsynaptic step for their induction also require some form of retrograde communication from the postsynaptic to the presynaptic cell (Fig. 1). Such communication is typically mediated by diffusible retrograde messengers, substances that are released on activity from dendrites and the cell body of neurons and, by targeting the presynaptic terminals, modify transmitter release in a long-lasting manner (Tao and Poo 2001; Regehr et al. 2009). Extensive experimental evidence shows that this mechanism is involved in several forms of presynaptic LTP/LTD at both excitatory and inhibitory synapses (Table 1). A wide range of retrograde messengers have been identified in the brain, including lipid derivatives, gases, peptides, conventional transmitters (e.g., glutamate and GABA), and growth factors (Regehr et al. 2009). Release of retrograde messengers is usually triggered by postsynaptic Ca^{2+} rises, but Ca^{2+} -independent release can also occur. Depending on their chemical nature, retrograde messengers are released in a vesicular or nonvesicular manner. Although there is good agreement

that some of these messengers play an essential role in triggering presynaptic LTP/LTD, the ultimate effectors mediating such changes are commonly unknown. A much less explored mechanism, albeit with potentially great relevance for presynaptic forms of plasticity, involves adhesion proteins that span the synaptic cleft (Futai et al. 2007; Gottmann 2008). Little is known about this transsynaptic mechanism in LTP/LTD beyond a few examples (Contractor et al. 2002; Armstrong et al. 2006) and it will not be considered further here.

The idea that retrograde signaling could mediate long-term synaptic plasticity LTP in particular is not new. This mechanism received a great deal of attention in the early 1990s during an intense “pre vs. post” debate regarding the expression locus of NMDAR-dependent LTP. Several diffusible retrograde messengers emerged as mediators of this form of plasticity, including arachidonic acid (Williams et al. 1989), platelet-activating factor (Kato et al. 1994), and gases such as carbon monoxide and nitric oxide (NO) (Zhuo et al. 1993, 1994; Son et al. 1996; Hawkins et al. 1998). Not surprisingly, in the field of synaptic plasticity many of the studies providing experimental evidence for these messengers also generated a great deal of controversy and contradictory results. To mention just one example, NO was strongly implicated as being the retrograde messenger mediating LTP at the Schaffer collateral to CA1 pyramidal cell synapse (for a recent review, see Feil and Kleppisch 2008). However, subsequent studies not only challenged the experimental evidence, but even the need for a retrograde signal in this form of LTP (for a review on this topic, see Kerchner and Nicoll 2008). It is worth noting that classical NMDAR-dependent LTP is not a homogenous phenomenon, and temporally overlapping processes that include a slowly developing presynaptic component and rapidly developing postsynaptic component have been identified (Lisman and Raghavachari 2006; Bayazitov et al. 2007). Although the early postsynaptically expressed phase may occur in the absence of retrograde signaling, such signaling may be important for a late presynaptically expressed LTP (Bayazitov et al. 2007).

The interest in retrograde signaling in presynaptic forms of LTP/LTD has intensified in recent years with the discovery of novel retrograde messengers as mediators of synaptic plasticity and the growing recognition of their widespread nature (Alger 2002; Regehr et al. 2009). In addition, retrograde signaling mediates multiple forms of long-term plasticity at inhibitory synapses throughout the brain, certainly expanding the number of synapse expressing presynaptic LTP/LTD (Castillo et al. 2011). As discussed above, there are several forms of presynaptic LTP/LTD, at both excitatory and inhibitory synapses, where the action of a retrograde messenger is assumed. Here, presynaptic forms of LTP/LTD mediated by an identified retrograde messenger will be briefly discussed.

Endocannabinoid-Mediated LTD

Endocannabinoids (eCB) mediate one of the clearest examples of presynaptically expressed LTD in the brain (Heifets and Castillo 2009). These retrograde messengers are lipids synthesized from membrane precursors, and two of the best characterized eCBs are N-arachidonoylethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG). Neuronal activity releases eCBs from the postsynaptic compartment, which travel backward to activate the presynaptic type 1 cannabinoid receptor (CB1R, a $G_{i/o}$ protein coupled receptor widely expressed in the brain), thereby suppressing neurotransmitter release at both glutamatergic and GABAergic synapses in a transient and a long-term manner (Chevalyere et al. 2006; Kano et al. 2009). Multiple examples of eCB-mediated LTD (eCB-LTD) have been identified throughout the mammalian brain (see Table 1) (Heifets and Castillo 2009). Although the pattern of afferent activity may differ between brain regions, induction of eCB-LTD typically begins with a transient increase in activity at glutamatergic afferents and a concomitant postsynaptic release of eCBs from a target neuron. By an unclear mechanism that may include an unidentified membrane transporter, eCBs then travel retrogradely across the synaptic cleft to activate CB1Rs on the presynaptic terminals of either

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the original glutamatergic afferent (homosynaptic eCB-LTD) or nearby GABAergic afferents (heterosynaptic eCB-LTD) (Chevalleyre et al. 2006). eCB release occurs via two separate postsynaptic processes (Piomelli 2003), activation of G_q -protein coupled metabotropic receptors (typically group I mGluRs and muscarinic acetylcholine receptors) and depolarization-induced Ca^{2+} influx via VGCCs. Both pathways contribute to eCB-LTD induction (Heifets and Castillo 2009). The metabotropic pathway engages phospholipase C (PLC) and diacylglycerol lipase (DGL), which produce the eCB 2-AG. Most forms of eCB-LTD require postsynaptic Ca^{2+} increase, which likely facilitates eCB production by activating Ca^{2+} -dependent enzymes, including PLC. Importantly, the metabotropic and Ca^{2+} -driven mechanisms can act independently, or synergistically to promote eCB release and eCB-mediated plasticity (Hashimoto et al. 2007; Heifets and Castillo 2009).

At the presynaptic side, CB1R activation is required for eCB-LTD induction but once plasticity is established it becomes CB1R-independent (Chevalleyre and Castillo 2003; Ronesi et al. 2004). Typically, induction of eCB-LTD requires that CB1Rs be activated for several minutes (Chevalleyre et al. 2006), suggesting that a slow, and probably metabolic process must occur at the presynaptic terminal for eCB-LTD consolidation. Because eCB-LTD requires PKA activity (Chevalleyre et al. 2007; Mato et al. 2008), and CB1Rs are negatively coupled to cAMP/PKA, such process is likely mediated by the $\alpha_{i/o}$ limb of the CB1R G-protein signaling cascade. Of note, transient activation of CB1Rs suppresses transmitter release by inhibiting presynaptic VGCCs, an effect likely mediated by the $G_{\beta\gamma}$ limb (Wilson et al. 2001). Another relevant property of eCB-LTD is that CB1R activation alone may not be sufficient for induction (Heifets and Castillo 2009). In neocortex, using spike timing-dependent protocols of induction, it has been shown that coincident activation of preNMDARs is also required (Sjöström et al. 2003; Bender et al. 2006; Nevian and Sakmann 2006). Presynaptic activity is also necessary for induction in the

hippocampus (Heifets et al. 2008) and dorsal striatum (Singla et al. 2007). Together, these observations suggest that Ca^{2+} influx via pre-NMDARs in neocortex, or via presynaptic VGCCs in hippocampus and dorsal striatum, may contribute to the PKA-dependent metabolic process mediating eCB-LTD. In support of this possibility is the observation that induction of eCB-LTD in the hippocampus also requires the activation of the Ca^{2+} -sensitive phosphatase calcineurin, likely shifting the balance of kinase (e.g., PKA) and phosphatase activity in the presynaptic terminal (Heifets et al. 2008). Finally, CB1Rs can interact with other signaling systems to regulate eCB-LTD induction. CB1R and type 2 dopamine receptor (D2R), which share a common signaling pathway by inhibiting adenylyl cyclase, act synergistically to induce eCB-LTD of inhibitory transmission in the prefrontal cortex (Chiu et al. 2010) and ventral tegmental area (Pan et al. 2008). In contrast, BDNF/TrkB signaling, presumably by inhibiting CB1R function, suppresses eCB-LTD induction at excitatory synapses in visual cortex (Huang et al. 2008). These examples clearly illustrate how multiple interactions between modulatory systems can occur at the presynaptic terminal to regulate eCB-LTD induction.

Retrograde Signaling beyond Endocannabinoids

Recent studies have provided additional evidence in support of previously identified retrograde messengers as mediators of unconventional forms of presynaptically expressed LTP/LTD. In the hippocampus, a form of presynaptic LTD on CA1 interneurons known to require retrograde signaling for induction (McMahon and Kauer 1997), has recently been reported to be mediated by a derivative of arachidonic acid acting on presynaptic TRPV1 channels (Gibson et al. 2008). This form of plasticity is triggered by HFS of Schaffer collaterals, the same induction protocol typically used to trigger LTP at Sch-CA1 synapses. Activation of postsynaptic group I mGluRs by glutamate released during tetanus generates arachidonic acid, which is

rapidly converted to 12-(S)-HPETE by 12-lipoxygenase. 12-(S)-HPETE is a membrane-permeable lipid with a short half-life that travels retrogradely across the synapse, in which it activates TRPV1 receptors on presynaptic glutamatergic nerve terminals. Activation of TRPV1 receptors is necessary and sufficient for the induction of this form of LTD. The precise mechanism by which TRPV1 triggers a long-lasting reduction of glutamate release remains unknown but it has been speculated that Ca^{2+} entry through the TRPV1 channel could activate a signaling cascade responsible for LTD (Gibson et al. 2008). A similar form of TRPV1-dependent LTD has recently been reported in the developing superior colliculus (Maione et al. 2009). It is worth noting that 12-(S)-HPETE has also been implicated in mGluR-dependent LTD at hippocampal Sch CA1 synapses (Feinmark et al. 2003), a form of plasticity with a presynaptic component of expression (Bolshakov and Siegelbaum 1994; Oliet et al. 1997; Zakharenko et al. 2002). The potential 12-(S)-HPETE target(s) that mediate this form of LTD are also unknown.

Neurotrophins such as brain-derived neurotrophic factor (BDNF) have been shown to modulate both excitatory and inhibitory transmission (Lessmann et al. 2003; Lu 2003; Blum and Konnerth 2005). There is also evidence that BDNF can be secreted from dendritic compartments in response to neuronal activity to act as a retrograde messenger and regulate transmitter release (Du and Poo 2004; Magby et al. 2006; Kuczewski et al. 2010). Recent studies have provided evidence for a retrograde action of dendritically released BDNF to potentiate GABAergic release in the visual cortex (Inagaki et al. 2008), hippocampus (Gubellini et al. 2005; Sivakumaran et al. 2009) and optic tectum (Liu et al. 2007). Although the induction protocols vary between brain regions, a postsynaptic Ca^{2+} rise is invariably required, which presumably enables BDNF secretion (Lessmann et al. 2003). Although the long-lasting enhancement of GABA release likely results from the activation of presynaptic TrkB receptors by BDNF, how exactly TrkB/BDNF signaling enhances transmitter release is unknown. Notably, the

mentioned studies used preparations in early stages of development. Whether BDNF retrograde signaling could also mediate presynaptic plasticity in older animals remains unknown.

NO can also act as retrograde messenger to persistently increase GABA release onto dopaminergic neurons in the ventral tegmental area (Nugent et al. 2007, 2009), a brain region crucial for reward processing and drug addiction. As for eCB-LTD at inhibitory synapses, this form of inhibitory LTP is heterosynaptic as it is triggered by HFS of glutamatergic fibers. In this case, induction requires NMDAR activation, postsynaptic Ca^{2+} rise, NO release from the dopaminergic cell and cGMP signaling in the GABAergic terminal. How exactly cGMP persistently increases GABA release remains unknown. Interestingly, a single *in vivo* exposure to morphine abolishes inhibitory LTP in ventral tegmental slices 24 hours later (Nugent et al. 2007), an observation consistent with the notion that exposure to addictive drugs can alter synaptic plasticity in the brain reward pathway (Kauer and Malenka 2007). Of note, both LTP (Nugent et al. 2007) and LTD (Pan et al. 2008) of inhibitory transmission may be induced in the ventral tegmental area. Although the requirements for induction differ, both types are expressed presynaptically. Finally, an activity-dependent, long-lasting increase in GABA release via NO retrograde signaling has recently been reported in the thalamus (Bright and Brickley 2008), raising the possibility that a similar form of NO-dependent LTP of GABAergic transmission may occur in other brain areas.

Modulatory Role of Presynaptic Receptors

By regulating Ca^{2+} influx or some metabolic step downstream of Ca^{2+} influx, both ionotropic and metabotropic receptors at presynaptic terminals can modulate the inducibility of presynaptic LTP/LTD. Such modulation has been reported at several synapses expressing diverse forms of presynaptic plasticity. Once again, a good example can be found at the MF-CA3 synapse where both suppression and facilitation of

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plasticity has been reported. For example, activation of presynaptic GABA_B and κ opioid receptors by endogenously-released GABA and dynorphin, respectively, increases the induction threshold for MF-LTP (Weisskopf et al. 1993; Vogt and Nicoll 1999). In addition, presumably by activating presynaptic A1 receptors, adenosine can also depress MF-LTP induction (Alzheimer et al. 1991; see also Moore et al. 2003). Activation of presynaptic type II mGluRs by synaptically-released glutamate does not seem to regulate MF-LTP induction (Vogt and Nicoll 1999) but can depotentiate MF-LTP immediately after induction (Tzounopoulos et al. 1998; Chen et al. 2001). In contrast to these suppressive effects, several studies have shown that induction of MF-LTP can be facilitated by presynaptic kainate receptors (KARs) (for a recent review, see Contractor et al. 2011). How exactly presynaptic KARs facilitate MF-LTP remains to be elucidated.

Input-Specificity and Associativity in Presynaptic LTP and LTD

Like postsynaptic LTP/LTD, presynaptic LTP/LTD shows input-specificity and associativity, two properties making activity-dependent synaptic plasticity a good cellular model of learning. In cases requiring a retrograde messenger, the signal may diffuse and target unrelated synapses, thereby compromising input-specificity and degrading information processing. However, this theoretical possibility has not been supported experimentally. One way to ensure input-specificity is by combining retrograde signaling with presynaptic activity. This dual requirement has been shown for eCB-LTD in visual cortex (Sjöstrom et al. 2003), dorsal striatum (Singla et al. 2007), and hippocampus (Heifets et al. 2008). Similar requirements are observed for heterosynaptic associative LTP at cortico-lateral amygdala synapses, except that in this case, the signal is glutamate arising from neighboring thalamic terminals (Humeau et al. 2003). An additional mechanism underlying input-specificity can be found in cerebellar stellate cell neurons in which functional dendritic compartments preclude calcium diffu-

sion along dendrites, thereby imposing spatial constraints to the synaptically-driven production of eCBs that mediate LTD at parallel fiber to stellate cell neurons synapses (Soler-Llavina and Sabatini 2006).

Associativity has also been observed at the level of the retrograde signal production in which two coincident signals are required (Bender et al. 2006; Nevian and Sakmann 2006). PLC is likely the coincident detector, integrating glutamate release via group I mGluR activation and activity-driven postsynaptic Ca²⁺ rise (Hashimoto et al. 2007). Endogenous muscarinic acetylcholine receptor activation also acts as an associative signal for eCB-LTD induction in the dorsal cochlear nucleus (Zhao and Tzounopoulos 2011). These few examples illustrate how associativity is not an exclusive property of postsynaptic LTP/LTD.

EXPRESSION MECHANISMS

What changes take place at the presynaptic terminal to account for the long-lasting increase or decrease in transmitter release associated with presynaptic forms of LTP or LTD? Intensive work in this area has shown that answering this question is much harder than originally thought. An important constraint in presynaptic plasticity studies is the relatively small size of most typical presynaptic terminals in the CNS, making their accessibility for biochemical/molecular manipulations, and both long-term live imaging and electrophysiological recordings extremely difficult. Transmitter release is a particularly complex phenomenon that involves several steps and molecular players (Südhof 2004; Pang and Südhof 2010), allowing for multiple points of regulation (Atwood and Karunanithi 2002; Catterall and Few 2008; de Jong and Verhage 2009). Changes in transmitter release at central synapses can occur as a result of modifications in the probability of release (Pr) and the number of functional release sites. In turn, Pr is determined by several factors; including the amount of Ca²⁺ influx through presynaptic VGCCs, the distance between these channels and the Ca²⁺ sensor for vesicle release, presynaptic Ca²⁺ dynamics, functional state,



number and precise localization of synaptic vesicles. Transmitter release can occur in a univesicular or multivesicular manner, and the magnitude of the multivesicular release component can be altered during presynaptic plasticity (Bender et al. 2009). In addition to changes in Pr, “presynaptic unsilencing” (Voronin 1994; Kerchner and Nicoll 2008) could also contribute to plasticity. Indeed, studies using dentate granule cell autapses (Tong et al. 1996) and optical imaging of postsynaptic Ca^{2+} transients in slice culture (Reid et al. 2004) have shown that recruitment of new release sites could participate in MF-LTP. While in theory any of these mechanisms could be involved in presynaptic forms LTP and LTD, most evidence points to two key points of regulation—presynaptic action potential-induced Ca^{2+} influx and the downstream release machinery (Fig. 2).

Changes in Presynaptic Calcium

Ca^{2+} ions play a crucial role in neurotransmission. Ca^{2+} influx via VGCCs triggers neurotransmitter release, and multiple mechanisms can regulate presynaptic VGCCs function (Catterall and Few 2008; Neher and Sakaba 2008). There is evidence that some forms of presynaptic LTP/LTD involve enduring changes in presynaptic Ca^{2+} influx. The best example can be found in the hippocampal mGluR7-dependent LTD at MF synapses on *s. lucidum* interneuron (MF-SLIN LTD, see above). Using two-photon

Ca^{2+} imaging from anatomically defined MF terminals and selective VGCC blockers, this form of LTD has been shown to be associated with a long-lasting depression of the presynaptic Ca^{2+} transient, which arises through a preferential depression of P/Q-type VGCCs and is blocked by an mGluR7 antagonist (Pelkey et al. 2006). How exactly mGluR7 activation produces irreversible depression of P/Q-type VGCCs remains unknown but it could involve PKC-dependent modulation of these channels (Perroy et al. 2000; Pelkey et al. 2005). A similar mechanism of expression mediated by presynaptic P/Q-type VGCCs has been reported in the nucleus accumbens. In this structure, two forms of presynaptic LTD at excitatory cortical inputs coexist (Table 1); one is induced by HFS and requires activation of presynaptic mGluR2/3 (Robbe et al. 2002a), whereas the other is triggered by moderate repetitive stimulation and requires activation of presynaptic CB1R (Robbe et al. 2002b; Mato et al. 2008). Both forms of LTD depend on cAMP/PKA signaling consistent with the fact that mGluR2/3 and CB1R are $G_{i/o}$ protein-coupled receptors. Remarkably, blockade of P/Q-type, but not of L- or N-type, VGCCs occludes both forms of LTD (Robbe et al. 2002a; Mato et al. 2008), which also mutually occlude (Mato et al. 2005), suggesting that mGluR2/3-LTD and eCB-LTD share a common mechanism.

Two recent studies suggest that long-lasting changes in presynaptic Ca^{2+} influx also underlie

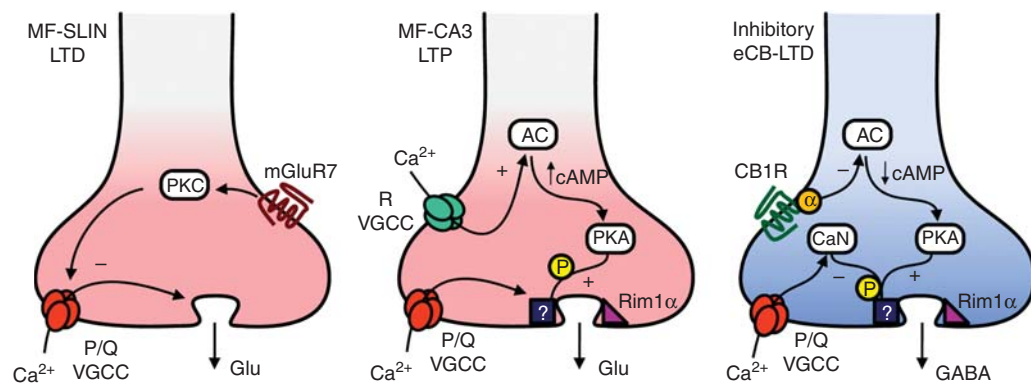


Figure 2. Expression mechanisms of presynaptic LTP and LTD: three prototypical examples (see text).

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presynaptic forms of LTP, but in this case L-type and N-type VGCCs seem to be involved. Indeed, using electrophysiological recordings and two-photon imaging of FM1-43 dye uptake and release at presynaptic terminals, one study showed that LTP at perforant path synapses in CA1 is associated with an enduring increase in the contribution of N-type VGCCs to transmitter release (Ahmed and Siegelbaum 2009). In contrast, the other study reported that presynaptic expression of associative LTP in lateral amygdala is caused by a persistent increase in L-type VGCC-mediated glutamate release (Fourcaudot et al. 2009), which is an intriguing observation given that presynaptic Ca^{2+} influx at most synapses is mainly mediated by N-type and P/Q-type VGCCs, but not L-type VGCCs. Future studies are required to determine the role of VGCCs in the expression of other forms or presynaptic LTP.

A potential role of presynaptic Ca^{2+} influx in presynaptic LTP was also examined in the hippocampus at the MF-CA3 synapse. Using direct imaging of the action potential-dependent presynaptic Ca^{2+} transient in MF boutons, several studies have consistently shown that no change in presynaptic Ca^{2+} occurs following MF-LTP (Regehr and Tank 1991; Kamiya et al. 2002; Reid et al. 2004). Similarly, no changes in Ca^{2+} transients were observed in the cerebellum following cAMP-mediated potentiation of parallel fiber to Purkinje cell synaptic transmission (Chen and Regehr 1997), a chemical form of plasticity that mimics synaptically-induced PF-LTP (Salin et al. 1996a). Together, these studies show that the long-lasting enhancement of transmitter release, at least at these synapses, must occur downstream from Ca^{2+} entry.

Finally, indirect changes in Ca^{2+} entry through VGCCs can occur as a result of modifications in the presynaptic action potential waveform. Although modulations in the excitability of the presynaptic terminal as a mechanism of synaptic plasticity have been well documented in invertebrates (for a recent review, see Glanzman 2010), the evidence for such a mechanism underlying presynaptic LTP or LTD in vertebrates is rather scarce.

Changes in the Release Machinery

The other major mechanism for regulating neurotransmitter release is via modulation of the molecular machinery responsible for synaptic vesicle exocytosis. Given the large number of proteins involved in this complex process, several candidate proteins could potentially mediate long-term synaptic plasticity, and some of them have been directly tested mainly using gene knockout approaches. One way to modulate function of these proteins is by protein phosphorylation (Leenders and Sheng 2005; de Jong and Verhage 2009). Because of the key role of cAMP/PKA signaling in multiple forms of presynaptic LTP and LTD (see above), most attention has been directed to presynaptic proteins known to be substrates for PKA (Seino and Shibasaki 2005). Among these proteins, synapsins (Spillane et al. 1995), rabphilin (Schlüter et al. 1999) and tomosyn (Sakisaka et al. 2008) have been shown to play no role in presynaptic MF-LTP. In contrast, the active zone protein RIM1 α has emerged as a key player not only in MF-LTP but also several others forms of presynaptic plasticity (Kaeser and Sudhof 2005). Interestingly, deletion of RIM1 α is associated with significant cognitive deficits (Powell et al. 2004). RIM1 α is a large multidomain protein that forms a scaffold at the presynaptic active zone and interacts with multiple presynaptic proteins. As a result, RIM1 α is in a strategic position to modulate transmitter release (Koushika et al. 2001; Schoch et al. 2002). Indeed, RIM1 α has been shown to be necessary for several cAMP/PKA-dependent forms of presynaptic plasticity including, MF-LTP (Castillo et al. 2002), cerebellar PF-LTP (Castillo et al. 2002), MF-SLIN LTP or de-depression (Pelkey et al. 2008), associative LTP in lateral amygdala (Fourcaudot et al. 2008), late LTP at Sch-CA1 synapses (Huang et al. 2005), GABAergic LTP at stellate cells in cerebellum (Lachamp et al. 2009), and inhibitory eCB-LTD in the hippocampus and amygdala (Chevalere et al. 2007). In addition, RIM1 α is a putative effector for the synaptic vesicle protein Rab3A, a protein essential for MF-LTP (Castillo et al. 1997), MF-LTD (Tzounopoulos et al. 1998), and late-LTP

in CA1 (Huang et al. 2005). The mechanism emerging from these studies is that increases of PKA activity and RIM1 α phosphorylation leads to LTP, whereas a reduction of PKA activity, in conjunction with phosphatase activity, dephosphorylates RIM1 α , which results in LTD. However, recent studies have challenged this simplistic model by demonstrating that mutation of serine-413, the RIM1 α phosphorylation site by PKA that has reported to be necessary for presynaptic LTP in parallel fiber synapses formed in vitro by cultured cerebellar neurons (Lonart et al. 2003), had no effect on MF-LTP, PF-LTP and eCB-LTD at inhibitory synapses (Kaesler et al. 2008; Yang and Calakos 2010). This observation is consistent with the fact that the presynaptic enhancement of synaptic transmission following transient activation of adenylyl cyclase is unaltered in knockout mice lacking Rab3A or Rim1 α (Castillo et al. 1997, 2002). Together, these findings argue that, although the RIM1 α complex is essential for presynaptic long-term plasticity, PKA regulates this type of plasticity by a mechanism distinct from RIM1 α phosphorylation at serine 413. In fact, PKA-dependent modulation of transmitter release can occur as a result of the phosphorylation/ dephosphorylation of several other presynaptic proteins involved in exocytosis (Seino and Shibusaki 2005; de Jong and Verhage 2009). Future studies are necessary to identify the nature of such a presynaptic protein(s) in PKA-dependent and RIM1 α -dependent forms of plasticity. Remarkably, not all forms of presynaptic LTP/LTD require cAMP/PKA signaling, and as a result, the number of candidate presynaptic proteins putatively involved in synaptic plasticity may be larger than expected.

CONCLUSIONS, CHALLENGES, AND FUTURE DIRECTIONS

More than two decades of research unequivocally showed that long-term presynaptic plasticity at excitatory and inhibitory synapses is widely used throughout the brain. Although some learning rules for presynaptic LTP and LTD are now understood, many questions re-

main to be elucidated. Chief among them is the precise molecular pathways underlying presynaptic plasticity. Although some key “players” have been identified, there are several loose ends. Presynaptic and postsynaptic LTP/LTD can coexist, and often times their induction differs, but in some cases overlap. It is unclear how these different forms of plasticity interact and how they contribute to information processing.

The retrograde signal involved in the induction of multiple forms of presynaptic LTP/LTD needs to be identified. Although most studies focused on presynaptic LTP/LTD induction and expression, much less is known about the maintenance and reversibility. Moreover, protein synthesis seems to be required for presynaptic plasticity at the MF-CA3 synapse (Huang et al. 1994; Calixto et al. 2003; Barnes et al. 2010) and in the dorsal striatum (Yin et al. 2006), and there is evidence that protein synthesis can occur in the presynaptic compartment (Giuditta et al. 2002; Yin et al. 2006; Barnes et al. 2010). The role of the newly synthesized proteins and their potential contribution to putative structural changes in presynaptic plasticity remains largely unexplored. Other future research areas include the potential contribution of glia, interactions between various modulatory systems and metaplasticity of presynaptic LTP/LTD.

Perhaps the most difficult challenge ahead is to understand how presynaptic long-term plasticity contributes to behavior. Accumulating evidence strongly suggest that presynaptic forms of plasticity can underlie some forms of learning. A good example can be found in the amygdala where presynaptic LTP and LTD are known to contribute to fear memory (Maren 2005; Sigurdsson et al. 2007; Sah et al. 2008; Pape and Pare 2010). The link between plasticity and behavior in other brain areas is assumed and more difficult to show. Synaptic plasticity is typically studied in brain slices, often times using relatively nonphysiological induction protocols and recording conditions. Although an extremely powerful experimental model to address mechanistic questions, the concepts developed from slice physiology need to be tested in intact animal preparations to fully understand

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the contribution of presynaptic forms of plasticity to behavior.

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