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Long-Term Plasticity of Neurotransmitter Release: Emerging Mechanisms and Contributions to Brain Function and Disease

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Abstract

Long-lasting changes of brain function in response to experience rely on diverse forms of activity-dependent synaptic plasticity. Chief among them are long-term potentiation and long-term depression of neurotransmitter release, which are widely expressed by excitatory and inhibitory synapses throughout the central nervous system and can dynamically regulate information flow in neural circuits. This review article explores recent advances in presynaptic long-term plasticity mechanisms and contributions to circuit function. Growing evidence indicates that presynaptic plasticity may involve structural changes, presynaptic protein synthesis, and transsynaptic signaling. Presynaptic long-term plasticity can alter the short-term dynamics of neurotransmitter release, thereby contributing to circuit computations such as novelty detection, modifications of the excitatory/inhibitory balance, and sensory adaptation. In addition, presynaptic long-term plasticity underlies forms of learning and its dysregulation participates in several neuropsychiatric conditions, including schizophrenia, autism, intellectual disabilities, neurodegenerative diseases, and drug abuse.

Keywords

LTP; LTD; structure; function; homeostatic; modulation; presynaptic

INTRODUCTION

The cellular basis of learning and memory is one of the greatest unsolved mysteries in neuroscience. Memory is believed to be stored in neuronal engrams, or specific subsets of synaptically-connected, coactive neurons, which are dynamically assembled via activity-dependent strengthening or weakening of synapses (Buzsaki 2010, Poo et al. 2016). Understanding how memories are preserved in the presence of various forms of plasticity is of great interest (Chaudhuri & Fiete 2016, Deneve et al. 2017). By expressing multiple

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forms of activity-dependent synaptic plasticity in space and time, individual neuronal responses can be optimized to allow for storage, transmission and recall of information (Costa et al. 2017). Synaptic plasticity therein endows networks with the robustness, redundancy and flexibility to independently adapt to changes in the environment.

Presynaptic plasticity is one form of plasticity generally defined as activity dependent modulation of neurotransmitter release. It can regulate circuit function over different timescales. Many studies have focused on short term presynaptic plasticity, which lasts for seconds to minutes (Regehr 2012), but much less is known about presynaptic changes that occur over hours, days, or even longer. Presynaptic long-term potentiation (preLTP) and presynaptic long-term depression (preLTD) of neurotransmitter release typically persist for hours, are widely expressed in the central nervous system (CNS) by both excitatory and inhibitory synapses, and are commonly due to changes in neurotransmitter release probability (P_r) (Castillo 2012,Yang and Calakos 2013). Despite significant advancements in the molecular basis of neurotransmission, exactly how transmitter release is modified in a long-term manner remains largely unclear. Although several molecular targets have been identified, the mechanisms governing preLTP and preLTD are known to be diverse and vary by brain region and cell type. Long-lasting changes in transmitter release can also occur as a synaptic adjustment in response to network activity, and such homeostatic plasticity occurs over hours to days. Silencing and unsilencing of presynaptic terminals are additional ways by which neurons persistently change their strength, but little is known about the underlying mechanisms and functional relevance. PreLTP and preLTD coexist with mechanistically distinct forms of activity-dependent plasticity, including postsynaptic LTP and LTD, which typically involves changes in receptor numbers or properties. A key question is why some synapses undergo presynaptic plasticity while others undergo postsynaptic plasticity or both. Does the distribution of presynaptic versus postsynaptic plasticity reflect a differential computational requirement? Long-term presynaptic plasticity can contribute uniquely to circuit computations by providing a way to modify short-term synaptic dynamics (i.e. by changing P_r). Lastly, what is the specific contribution of preLTP and preLTD to behavior and brain disease? Here, we address these fundamental questions and review emerging mechanisms of presynaptic long-term plasticity with the goal of elucidating its contribution to brain function.

MOLECULAR BASIS OF PRESYNAPTIC PLASTICITY

The induction mechanisms of preLTP and preLTD typically involve transient increases of presynaptic Ca^{2+}, activation of presynaptic receptors and metabolic cascades, and retrograde signaling from the postsynapse. These processes are highly regulated, allowing for metaplasticity, the plasticity of synaptic plasticity, and input specificity, which refers to information storage at particular subsets of synapses (for a review of induction mechanisms and their regulation, see Castillo 2012). How neurotransmitter release is changed in a long-term manner during preLTP or preLTD is less clear. The tightly packed presynaptic terminal hosts thousands of different proteins that modulate neurotransmitter release (Figure 1). Molecules involved in basal transmission or short-term plasticity, as well as plasticity-specific proteins, may also have a role in long-term plasticity. These molecules regulate

many different presynaptic processes which are critical to the expression of preLTP and preLTD, such as Ca^{2+} signaling, and synaptic vesicle exocytosis and endocytosis.

Presynaptic Ca^{2+}

Ca^{2+} has a critical role in neurotransmitter release and presynaptic plasticity. Presynaptic Ca^{2+} triggers soluble N-ethylmaleimide sensitive fusion protein (NSF) attachment protein receptor (SNARE)-mediated synaptic vesicle fusion via a low-affinity (micromolar range) process. A second, high-affinity Ca^{2+} sensor, distinct from the Ca^{2+} channel or fusion machinery, has been proposed to underlie synaptic facilitation, a seconds-long increase of transmission, in response to residual Ca^{2+} following repetitive activity (Jackman & Regehr 2017). Changes in action potential waveform can modulate presynaptic voltage-gated Ca^{2+} channel (VGCC) kinetics, Ca^{2+} influx, and transmitter release. Ca^{2+} also regulates G protein--coupled receptor (GPCR) second-messenger cascades involved in presynaptic long-term plasticity (Atwood et al. 2014). PreLTP and preLTD can rely on the recruitment of specific VGCCs. For example, hippocampal preLTP relies on N-type channels (Ahmed & Siegelbaum 2009), whereas amygdalar preLTP relies on L-type channels (Fourcaudot et al. 2009). PreLTD at the hippocampal mossy fiber (MF)-interneuron synapse involves presynaptic $G_{i/o}$-coupled metabotropic glutamate receptor 7 (mGluR7)-mediated reduction in P/Q-type Ca^{2+} transients (Pelkey et al. 2006). A similar mechanism for preLTD in the nucleus accumbens (NAc) relies on presynaptic $G_{i/o}$-coupled cannabinoid-1 ($CB_{1)}$ and mGluR2/3 receptors signaling (Mato et al. 2008, Robbe et al. 2002). Certain VGCC subtypes are tightly coupled (nanodomain) to the release machinery, whereas others are loosely coupled (microdomain) (Eggermann et al. 2011). Tight versus loose coupling is regulated by scaffolding proteins such as Rab-interacting molecules (RIMs) and RIM-binding proteins that tether VGCCs near the active zone (AZ) to ensure the fidelity of synaptic transmission (Acuna et al. 2015, Han et al. 2011). Changes in the clustering of or physical distance between VGCCs and the release site, as was recently demonstrated in the developing Calyx of Held synapse (Nakamura et al. 2015), could significantly affect the induction and expression of presynaptic long-term plasticity. Therefore, modulating presynaptic Ca^{2+}, at the level of its influx, channel kinetics, or coupling, is an important mechanism of presynaptic plasticity. More work is needed to understand how Ca^{2+} microdomains are regulated by activity to impact neurotransmitter release in a long-term manner.

Release Machinery

Numerous studies have linked activity-dependent signaling to long-term changes in transmitter release (Castillo 2012, Yang and Calakos 2013). During induction, the rise in intraterminal Ca^{2+} or the activation of presynaptic receptors triggers a signaling cascade involving a web of kinases and phosphatases. These events can directly modify the release machinery or engage second messengers to indirectly alter release. Because cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling has a key role in multiple forms of preLTP and preLTD (Castillo 2012), many studies have focused on presynaptic PKA substrates. Among these are the AZ-scaffolding protein RIM1α, which is critical for preLTP and preLTD at excitatory and inhibitory synapses (Castillo 2012). RIM1α interacts with synaptic vesicle--associated proteins Rab3A and Rab3B, which have also been implicated in

preLTP and preLTD, but it remains unclear how the Rab3/RIM1α complex is activated because its phosphorylation by PKA does not seem to be required for presynaptic long-term plasticity.

PKA phosphorylation of the synaptic vesicle protein synaptotagmin-12 is required for LTP at the MF-to-CA3 pyramidal cell synapse (MF-LTP) but not for short-term plasticity or endocannabinoid (eCB)-mediated LTD of inhibition (iLTD) (Kaeser-Woo et al. 2013), a form of presynaptic plasticity that also relies on PKA signaling (Castillo 2012). Intriguingly, genetic ablation of the PKA-anchoring protein AKAP7 from MFs abolishes chemically induced but not synaptically induced LTP (Jones et al. 2016), consistent with recent evidence that Epac2, another cAMP effector, contributes significantly to MF-LTP (Fernandes et al. 2015). Activation of presynaptic $G_{i/o}$ protein--coupled mGluR2/3 and CB_1 receptors, presumably by reducing cAMP/PKA activity, typically leads to long-lasting reduction in neurotransmitter release but the molecular target is unknown (Atwood et al. 2014). Phosphorylation of synaptosomal-associated protein 25 (SNAP-25) (Katayama et al. 2017) and complexin (Cho et al. 2015) is implicated in short-term presynaptic plasticity and these proteins may also be targets for long-term plasticity. In addition, it remains unclear whether changes in phosphorylation activity persist throughout preLTP and preLTD or whether other mechanisms account for the long-lasting change in neurotransmitter release. In theory, any protein that participates in the release machinery could be an activity-dependent target for presynaptic plasticity via phosphorylation or local synthesis/degradation.

The signaling cascades triggering phosphorylation events that result in presynaptic changes operate in a highly synapse-specific manner. For example, CB_1 receptor-mediated depression of transmission at CA3-CA1 synapses is mediated by extracellular signal--regulated kinase (ERK) phosphorylation and subsequent degradation of Munc18, a key regulator of vesicle fusion (Schmitz et al. 2016). In contrast, at the lateral perforant path, CB_1 receptors signal via β1-integrins to mediate preLTP (W. Wang et al. 2017). At hippocampal inhibitory synapses, eCB-mediated iLTD requires activation of the mammalian target of rapamycin (mTOR), rather than ERK, and presynaptic protein synthesis (Younts et al. 2016). Thus, the (de)phosphorylation events that mediate long-term changes in neurotransmitter release can depend on the brain region and synapse type. Future research should determine to what extent molecular signaling is generalizable or unique to presynaptic plasticity.

EMERGING MECHANISMS OF PRESYNAPTIC PLASTICITY

Beyond changes in presynaptic Ca^{2+}signaling and the release machinery, recent studies have begun to reveal novel mechanisms that contribute to preLTP and preLTD. These include presynaptic changes in axonal bouton structure, protein synthesis and degradation, energy metabolism, transsynaptic cell adhesion proteins and signaling via astrocytes. The emerging picture is that long-term presynaptic plasticity is mechanistically more diverse than originally thought (Monday & Castillo, 2017).

Presynaptic Structural Plasticity

The size of the AZ and postsynaptic density (PSD) are proportional to synapse strength, suggesting that functional and structural plasticity are interdependent and structural changes are somehow coordinated across the synapse (Meyer et al. 2014, Petzoldt et al. 2016). As is the case for dendritic spines, growing evidence indicates presynaptic terminals undergo activity-dependent structural changes (Sigrist & Schmitz 2011). Presynaptic plasticity may involve the insertion or removal of AZ release sites, vesicle pool redistribution, changes in overall terminal size (Petzoldt et al. 2016), or small changes in protein clustering at the AZ (Figure 2*a*).

Axon terminal morphological plasticity is widespread during critical periods and in adulthood (Gogolla et al. 2007, Holtmaat & Caroni 2016). At the giant hippocampal MF boutons, presynaptic morphological complexity, e.g. bouton segmentation, was correlated with increased postsynaptic response size and environmental enrichment (Galimberti et al. 2006, Gogolla et al. 2009). Similarly, high-frequency stimulation in organotypic cultures increased segmentation of the giant bouton, which depended on postsynaptic glutamate receptor activation, Ca^{2+} rise, and retrograde signaling via nitric oxide (NO) and arachidonic acid (Maruo et al. 2016). Persistent increases in presynaptic complexity may allow synchronization of release sites via enhanced VGCC coupling to produce long-term changes in neurotransmitter release.

Classical postsynaptic LTP in CA1 is associated with presynaptic ultrastructural changes at Schaffer collateral axons. Boutons with a single postsynaptic partner are reduced in number, and the remaining synapses are enlarged and contain fewer vesicles, suggesting a homeostatic constraint on the total amount of synaptic area in the brain (Bourne et al. 2013). The induction of LTD in hippocampal slice cultures has also been associated with presynaptic structural changes, such as fewer synaptic contacts and an increased turnover rate of presynaptic boutons (Becker et al. 2008). Moreover, a significant proportion of inhibitory axon boutons, appear, disappear, and reappear at specific locations not only in vitro (Schuemann et al. 2013) but also in vivo (Villa et al. 2016). Many factors, including synapse strength, type, location, cell identity, animal age, and network state, likely determine the relative stability of some boutons over others (Gogolla et al. 2007, Holtmaat & Caroni 2016). More work is needed to determine the precise contribution of each factor to structural plasticity.

Actin depolymerization and polymerization can drive presynaptic structural remodeling by altering the underlying cytoskeleton (Michel et al. 2015). Actin is organized around synaptic vesicles and undergoes activity-dependent remodeling such that actin is recruited to the bouton following vesicle mobilization (Sankaranarayanan et al. 2003). β-Actin and γ-actin are critical for both slow and bulk endocytosis at small CNS synapses (Wu et al. 2016), and proteins that regulate actin dynamics in an activity-dependent manner have been implicated in presynaptic plasticity (Cingolani & Goda 2008). Mammalian homolog of Diaphanous (mDia) and Rho-associated coiled-coil-containing kinase (ROCK), two Rho-regulated modulators of the actin cytoskeleton, participate in actin remodeling of the presynaptic terminals of NAc neurons as a result of social isolation (Deguchi et al. 2016). Additional actin-modulating proteins such as Profilin2 (Pilo Boyl et al. 2007) and Cyfip1 (Hsiao et al.

2016) regulate neurotransmitter release on short timescales, but their involvement in long-term plasticity is still unknown.

Axonal Proteostasis

Local synaptic protein synthesis endows remote neuronal compartments with the ability to rapidly respond and adapt to local cues (Alvarez et al. 2000). For many years, researchers thought that healthy adult mammalian CNS axons were not capable of synthesizing proteins. Indirect evidence suggested a role for protein synthesis in certain forms of preLTP and preLTD (Monday & Castillo 2017). Recent studies used super-resolution and electron microscopy to reveal ribosomes in healthy adult axon terminals (Shigeoka et al. 2016, Younts et al. 2016) (Figure 2*b*). Messenger RNA (mRNA) and mRNA-binding proteins have also been observed in adult axons (Akins et al. 2017). Functionally, axonal protein synthesis is required for eCB-mediated iLTD in the hippocampus (Younts et al. 2016). Activity-dependent axonal protein synthesis seems to trigger a molecular switch that regulates P_r and transmitter release. The identity of the synthesized protein(s) remains unknown, and it is unclear how widespread axonal protein synthesis is in the mature CNS.

By selective, local protein degradation, the proteasome and lysosome also have critical roles in presynaptic plasticity (Hegde 2017, Y.C. Wang et al. 2017). Selectivity of these systems can be achieved by specific localization or expression of adaptor proteins that target substrates for degradation or of the degradation machinery itself (Hegde 2017). For example, at Schaffer collaterals, activity-dependent proteasomal degradation of Munc18 was proposed to underlie CB_1-mediated depression (Schmitz et al. 2016, W. Wang et al. 2017). In addition, proteasomal activation was linked to presynaptic silencing (see below) via RIM1α and Munc13–1 degradation (Jiang et al. 2010). The extent of protein degradation likely determines whether a synapse undergoes LTD, silencing, or bouton retraction or removal, but how synaptic activity leads to proteasome activation is not clear.

Transsynaptic Cell Adhesion Molecules

Transsynaptic cell adhesion molecules (CAMs) are proteinaceous bridges that were first proposed to regulate synapse specificity and formation (Dalva et al. 2007, Jang et al. 2017). Synapse formation is a unique form of plasticity that occurs throughout life, but how neurons determine synapse position is poorly understood. Growing evidence indicates that CAMs are also involved in synaptic transmission and presynaptic plasticity, likely via actin cytoskeleton rearrangements (Frias & Wierenga 2013, Jang et al. 2017). For example, the induction of presynaptic MF-LTP requires transsynaptic EphB/ephrin-B3 signaling (Contractor et al. 2002). Membrane-anchored ephrin-B ligands interact with EphB receptors bidirectionally and modulate the cytoskeleton and release machinery recruitment (Sheffler-Collins & Dalva 2012). Likewise, the transsynaptic neurexin/neuroligin complex has also been implicated in modulating P_r at mature synapses (Krueger et al. 2012). α-neurexin is essential for Ca^{2+}-triggered transmitter release (Missler et al. 2003), and β-neurexin supports presynaptic, eCB-mediated LTP in the subiculum (Anderson et al. 2015). The transsynaptic modulation of P_r may involve neurexin signaling to Munc18, synaptotagmin, and/or VGCCs (Jang et al. 2017, Krueger et al. 2012). Similarly, postsynaptic neuroligin-2, which is expressed at GABAergic synapses (Varoqueaux et al. 2004), retrogradely regulates

inhibitory synaptic transmission (Gibson et al. 2009, Jedlicka et al. 2011, Varoqueaux et al. 2004). These findings suggest transsynaptic CAMs have an integral role in regulating synaptic strength across the synaptic cleft during preLTP and preLTD.

Recent studies using super-resolution microscopy have revealed a modular organization of the synapse, in which release sites and postsynaptic receptors appear to be aligned in transsynaptic nanocolumns (Figure 2*c*). Correlated RIM1/2 and PSD-95 nanoclusters are modulated by *N*-methyl-D-aspartate receptor (NMDAR) activation, resulting in distinct pre- and postsynaptic structural changes (Tang et al. 2016). Chemical LTD disrupted the PSD-95 columnar organization, after which the RIM1/2 cluster volume markedly increased, suggesting a retrograde signal could engage some sort of presynaptic homeostatic plasticity (Tang et al. 2016). Similarly, neuronal activation promoted clustering of the AZ matrix through a retrograde mechanism likely involving eCBs (Glebov et al. 2017). Long-term blockade of neuronal activity has the opposite effect, leading to AZ scaffold unclustering as well as actin depolymerization, enrichment of AZ machinery such as P/Q-type VGCCs, and reduced AZ-PSD distance (Glebov et al. 2017). Thus, synaptic geometry can be rapidly reorganized by activity, resulting in nanoscale changes in protein localization that may affect transmission in a long-term manner. These nanocolumns reflect an additional example of bilateral coordination of pre- and postsynaptic structures.

Presynaptic Energy Metabolism

Neurotransmitter release is a highly energy-demanding process. ATP is required to maintain ion gradients, power vesicle filling and cycling, and support enzymatic activity (Harris et al. 2012). Mitochondria supply energy, buffer Ca^{2+}, and are recruited to certain presynaptic terminals. Oxidative phosphorylation in mitochondria supplies the majority of ATP required for release (Rangaraju et al. 2014), but only approximately 40% or less of small CNS terminals contain mitochondria (Chavan et al. 2015, Smith et al. 2016). Levels of ATP can be sustained in boutons lacking mitochondria via glycolysis or axonal diffusion of mitochondrially-derived ATP (Pathak et al. 2015). Mitochondria localization may depend on synaptic energy demands because vesicle release, vesicle number, and PSD size are correlated with the presence and volume of mitochondria at terminals (Sun et al. 2013). Blocking mitochondria activity alters basal P_r, homeostatic, and synaptic plasticity (Harris et al. 2012). After inducing LTP, boutons that have mitochondria contain fewer vesicles (Smith et al. 2016), suggesting mitochondria regulate vesicle pool mobility during plasticity. Mitochondria themselves are motile, and their positioning also contributes to presynaptic homeostatic plasticity and synapse strength (Sun et al. 2013). Recent studies suggest that brain-derived neurotrophic factor (BDNF) and cannabinoids decrease presynaptic mitochondria mobility, which can enhance or depress transmitter release (Hebert-Chatelain et al. 2016, Su et al. 2014). Although energy metabolism is critical for neurotransmitter release, the activity-dependent modulation of mitochondrial localization and function as well as their role in supporting sustained changes in transmitter release deserve further attention.

Astrocytes

Astrocytes establish bidirectional interactions with neurons and have been implicated in presynaptic plasticity via gliotransmission (Min et al. 2012, Perea et al. 2009). Glutamate

release from astrocytes can increase neurotransmission by activating presynaptic NMDARs (Jourdain et al. 2007) and triggers preLTP by activating presynaptic mGluRs (Perea & Araque 2007). eCBs released from neurons can activate astrocytic CB_1 receptors that stimulate glutamate release from astrocytes. Astrocytic glutamate activates presynaptic NMDARs to induce neocortical preLTD (Min & Nevian 2012), whereas presynaptic group I mGluRs are engaged in hippocampal preLTP (Gómez-Gonzalo et al. 2015). Astrocytic CB_1 receptors also mediate release of astrocytic D-serine which is involved in hippocampal preLTD (Andrade-Talavera et al. 2016). Given the highly interconnected astrocytic syncytium, the requirement of coincident signals, such as astrocytic CB_1 engagement and postsynaptic receptor activation may help ensure input specificity of astrocyte-mediated plasticity.

ADDITIONAL FORMS OF PRESYNAPTIC PLASTICITY

Multiple forms of presynaptic plasticity can coexist in the same synapse, circuit, or brain region. In some cases, these forms of plasticity may involve similar mechanisms or timescales or they may wholly overlap with preLTP and preLTD, but how they interact remains unclear.

Presynaptic Homeostatic Plasticity

Homeostatic plasticity refers to compensatory adjustments of neuronal excitability toward a set point in the continued presence of a perturbation (Turrigiano 2012). This can be achieved via synaptic scaling and changes in intrinsic excitability and is thought to preserve computational capacity and the excitatory/inhibitory (E/I) balance of a given network. Homeostatic plasticity can also involve changes in neurotransmitter release (for a review, see Davis & Müller 2015). However, preLTP, preLTD, and presynaptic homeostatic plasticity are likely induced by distinct cues and operate over different timescales. Unlike induction of preLTP or preLTD, induction of homeostatic plasticity typically requires some long-lasting signal(s). Presynaptic homeostatic plasticity could manifest as changes in presynaptic ion channel expression, in neurotransmitter receptor surface expression and trafficking, and in the readily releasable pool (Davis & Müller 2015). Transsynaptic signaling has been implicated in this process. Given that some common mechanisms could underlie preLTP, preLTD, and homeostatic plasticity, how these forms of plasticity interact, or remain distinct, is an open question.

Presynaptic Silencing

Throughout the brain, a portion of presynaptic terminals are in a dormant state. They contain the structural hallmarks of an active terminal such as vesicles and SNARE proteins yet are release incompetent (Crawford & Mennerick 2012). Their function is unclear, but they are likely important substrates for plasticity (Atwood & Wojtowicz 1999, Voronin & Cherubini 2004). Persistent network depolarization homeostatically increases dormant glutamatergic terminals in cultured neurons (Moulder et al. 2004) in a $G_{i/o}$-dependent manner but independent of CB_1-, A1 adenosine-, and $GABA_B$- receptors (Crawford et al. 2011). Tonic CB_1 receptor activation is associated with muting a subset of GABAergic terminals in the hippocampus (Losonczy et al. 2004) and cerebellar granule cells (Ramírez-Franco et al.

2014). In the latter, CB_1 receptor activation silences release-competent synapses and triggers vesicle retraction from the AZ. Excitatory synaptic inputs onto motor neurons also show CB_1-mediated vesicle redistribution (García-Morales et al. 2015), suggesting a common mechanism of presynaptic silencing. Like preLTD, reducing cAMP signaling increases the dormant presynaptic terminal number, which is associated with decreased RIM1 levels (Jiang et al. 2010). Conversely, unsilencing is associated with actin remodeling (Yao et al. 2006), PKA activation (Bolshakov et al. 1997, Moulder et al. 2008), and protein synthesis (Ma et al. 1999). Despite these examples and mechanistic insights, the extent, duration, and functional significance of presynaptic silencing in the brain is still unclear.

IMPLICATIONS OF PRESYNAPTIC LONG-TERM PLASTICITY FOR CIRCUIT FUNCTION

The presynaptic or postsynaptic expression locus of plasticity has important implications for circuit computation (Costa et al. 2017). Although the precise relationship between presynaptic plasticity and computation is still being explored, some principles have emerged. The timing and rate of presynaptic activation make fundamental contributions to neuronal circuit operations (Abbott & Regehr 2004). Presynapses act like filters, permitting or preventing transmission depending on activity patterns, P_r, and short-term dynamics (Abbott & Regehr 2004). In this context, long-term plasticity of transmitter release can be viewed as a modification of basal P_r and short-term release dynamics. Presynaptic long-term plasticity of basal P_r can shift synapses between low-pass, band-pass, and high-pass filtering modes (Figure 3), thus altering the computational properties of the synapse. For example, synapses with low initial P_r, such as MFCA3 synapses, function like high-pass filters that attenuate single or low-frequency signals but readily transmit information occurring in high-frequency bursts. Synapses that operate in this mode are ideally suited for novelty detection, permitting the flow of activity generated by salient information through the circuit (Lisman 1997). In contrast, synapses with high initial P_r, such as cerebellar climbing fibers, exhibit low-pass filtering characteristics, preferentially transmitting information at the onset of presynaptic activity. Synapses with intermediate initial P_r, such as most central synapses, exhibit band-pass filtering and preferentially transmit information across a normal frequency distribution. Arguably, most redistribution of synaptic efficacy because of preLTP and preLTD (Markram & Tsodyks 1996, Sjostrom et al. 2003) is likely to occur in the band-pass range, having complex and subtle effects on circuit function. For example, changes in basal P_r may subtly shift the timing of the peak postsynaptic response. This likely influences the timing and dispersion (i.e., jitter) of postsynaptic spiking, which in turn may have significant consequences on the inducibility of spike- or burst-timing-dependent plasticity.

Diverse forms of synaptic plasticity (e.g., short-term and long-term, presynaptic and postsynaptic, strengthening and weakening of excitatory and inhibitory transmission) combine in complex ways to affect local circuit computations. These forms of plasticity also coexist with homeostatic mechanisms to maintain circuit function despite potentially destabilizing perturbations. Presynapses from the same neuron can express different forms of plasticity that partly depend on postsynaptic identity (Larsen & Sjöström 2015). Moreover, the synaptic learning rules for inducing LTP or LTD can change depending on the

state of the circuit. Neuromodulators can change overall network activity, alter plasticity induction thresholds and time windows, or even switch the plasticity sign from LTP to LTD (Froemke 2015, Hennequin et al. 2017). The coexistence of multiple forms of plasticity (e.g., presynaptic and postsynaptic) may reflect hierarchical processing of information, potentially allowing ordering of memory according to its salience (Shin et al. 2010).

Increasing P_r (e.g., preLTP of excitatory connections) increases trial-to-trial synaptic transmission reliability. For high-P_r synapses, this is nearly a one-to-one relay. In the CNS, most excitatory synapses have a lower initial P_r, and a single presynaptic spike does not lead to postsynaptic spiking, likely because the brain must both decipher and decode as well as ignore irrelevant information. The distribution of P_r across a population of inputs may be relevant for coding during sensory learning. For example, under baseline conditions before learning, auditory-evoked responses occur in the context of a noisy background of spontaneous activity, with responses comparable in size to those of other inputs (Froemke et al. 2013). Following long-term synaptic plasticity, small synaptic responses increased and large synaptic responses shrank. The average size of the sensory-evoked response remained constant, but the variance of responses decreased. These synaptic changes, which likely involve a redistribution of presynaptic weights, were correlated with improved sensory perception.

The regulation of E/I balance is one mechanism that can stabilize neuronal networks in the presence of synaptic and other forms of plasticity to preserve computational capacity. There is growing evidence that inhibitory plasticity, including preLTP and preLTD of GABA release (Castillo et al. 2011, Woodin & Maffei 2010), could have a key role in maintaining the E/I balance (Hennequin et al. 2017). In addition, inhibitory plasticity can partially disinhibit neurons, creating a window of opportunity for excitation and information flow (Basu et al. 2013, Younts et al. 2013). LTP of GABA release can occur as a result of retrograde signaling by BDNF and NO (Castillo et al. 2011), whereas LTD of GABA release is commonly mediated by retrograde eCB signaling (Castillo et al. 2012). Clearly, long-term presynaptic plasticity has emerged as a nuanced way to store, transmit and route information through circuits. Concerted efforts are needed to establish precisely how changes in presynaptic structure and function contribute to network performance and behavior.

PRESYNAPTIC LONG-TERM PLASTICITY AND BEHAVIOR

Determining the precise contribution of a given form of synaptic plasticity to brain function is extremely difficult. Establishing causality requires manipulations that specifically interfere and mimic plasticity in vivo, but such manipulations are rare. Here, we summarize a few examples that illustrate a potential role for preLTP and preLTD in behavior.

Although presynaptic forms of plasticity at the MF-CA3 synapse in vitro have been widely characterized, their relationship with cognition is not yet entirely clear. The high-pass filtering property of the MF-CA3 synapse is thought to help make patterns of neuronal activity distinct and unique to where an animal is located in the environment (Evstratova & Tóth 2014, Rebola et al. 2017). PreLTP and preLTD would have the dual effect of changing the high-pass filter cutoff frequency and signal-to-noise ratio, permitting or rejecting bursts

of incoming activity. Consistent with this idea, exposure to a novel environment facilitates LTP whereas addition of prominent landmarks facilitates LTD at the MF-CA3 synapse in vivo (Hagena & Manahan-Vaughan 2011). Many of the signaling molecules that have a role in preLTP and preLTD at MFCA3 synapses in vitro also contribute to cognitive tasks, including hippocampus-dependent associative learning paradigms. For example, RIM1α knockout mice were impaired in contextual fear conditioning, whereas Rab3A knockout mice could still learn (Powell et al. 2004) but their memory precision was impaired (Ruediger et al. 2011). The cognitive effect of selective deletion of RIM1α/Rab3A from presynaptic dentate granule cells is unknown. Genetic ablation of the PKA-anchoring protein AKAP7 specifically from dentate granule cells impaired both contextual fear conditioning and MF-CA3 preLTP initiated by cAMP/PKA activation in vitro (Jones et al. 2016). There is also evidence that experience and learning lead to MF terminal structural plasticity, including expansion of the axonal field and increase in the number of release sites (Galimberti et al. 2006, Gogolla et al. 2009, Ruediger et al. 2011).

In the amygdala, preLTP and preLTD contribute to fear memory formation (Tovote et al. 2015) in a synapse-specific manner. Lateral amygdala inputs from the cortex mainly express presynaptic cAMP/PKA-dependent LTP (Huang & Kandel 1998), but coactivation of cortical and thalamic afferents triggers presynaptic NMDAR-dependent associative LTP at cortical inputs (Humeau et al. 2003). These presynaptic forms of LTP contribute to amygdala-dependent fear memory (McKernan & Shinnick-Gallagher 1997). Fear learning also induces preLTP of lateral amygdala excitatory inputs onto somatostatin inhibitory interneurons in the central amygdala, and activation of these interneurons was sufficient to drive fear responses (Li et al. 2013). In contrast, preLTP at thalamic inputs onto local amygdala inhibitory interneurons is linked with fear suppression (Bauer & LeDoux 2004), whereas fear extinction in the amygdala appears to involve eCB-mediated iLTD (Lutz 2007, Azad et al. 2004). Fear extinction is also associated with LTD at excitatory inputs from the prefrontal cortex to basolateral amygdala (Cho et al. 2013). The relationship between excitatory and inhibitory plasticity in the amygdala is complex, but one hypothesis is that inhibition controls the level of presynaptic $GABA_B$ receptor activation to regulate nonassociative forms of preLTP and generalization of fear-conditioned stimuli (Shaban et al. 2006).

Although these examples clearly indicate that presynaptic plasticity is involved in certain behaviors, more specific tools designed to interfere directly with presynaptic function are needed, for example, by optically controlling neurotransmitter accumulation inside synaptic vesicles (Rost et al. 2015) or by manipulating the molecular composition of specific presynaptic terminals, as was recently done for postsynaptic signaling molecules involved in plasticity (Hayashi-Takagi et al. 2015, Sinnen et al. 2017).

PRESYNAPTIC PLASTICITY IN DISEASE

Neuropsychiatric disorders and degenerative diseases commonly involve insults to synapse structure and function (Volk et al. 2015). Here, we describe some examples of impaired presynaptic plasticity in animal models of brain diseases and identify molecular targets of potential therapeutic relevance.

Schizophrenia

Anomalous synaptic function, due to genetic and environmental factors, likely underlies schizophrenia (Crabtree & Gogos 2014). One of the highest risk factors for schizophrenia is the 22q11 microdeletion syndrome (Earls & Zakharenko 2014). A mouse model of 22q11, *Df(16)A*$^{+/-}$, shows an age-dependent enhancement in P_r, short-term plasticity, and LTP at hippocampal Schaffer collaterals, which coincides with deficits in spatial memory (Earls & Zakharenko 2014). *Df(16)A*$^{+/-}$ mice also exhibit decreased axonal branching in the prefrontal cortex and impaired hippocampus--prefrontal cortex oscillations (Mukai et al. 2015, Sigurdsson et al. 2010). This 22q11 mouse model also shows age-dependent deficits in social interaction, which was linked to presynaptic δ-opioid-iLTD in hippocampal CA2 (Piskorowski et al. 2016). The genes encoding neuregulin 1 (NRG1) and its receptor ErbB4 are schizophrenia susceptibility genes (Buonanno 2010). NRG1 signaling via ErB4 promotes GABA release, which impairs the E/I balance, LTP, and fear conditioning (Lu et al. 2014, Shamir et al. 2012, Woo et al. 2007). DISC1, a scaffolding protein associated with schizophrenia (Crabtree & Gogos 2014), can regulate the E/I balance via NRG1/ErbB4 signaling (Seshadri et al. 2015) and modulates presynaptic plasticity (Kvajo et al. 2011). Other schizophrenia-associated mutations affecting presynaptic long-term plasticity include microRNA-137 (Siegert et al. 2015) and RIM1α (Blundell et al. 2010). The etiology of schizophrenia involves many genes, some of which are expressed in postsynaptic compartments. Much more research is needed to untangle the relative contribution of genetic and environmental factors to synaptic dysfunction.

Autism and Intellectual Disability

Altered presynaptic plasticity has been reported in animal models of autism spectrum disorders. The most common heritable cause of autism is Fragile X syndrome, which results from *FMR1* gene transcription silencing (Darnell & Klann 2013). FMRP (fragile X mental retardation protein) is an mRNA-binding protein that negatively regulates expression of mRNAs, many of which encode presynaptic proteins (Darnell & Klann 2013). FMRP is expressed in a subset of synaptic terminals (Christie et al. 2009), where it may regulate vesicle release through local protein translation (Akins et al. 2017, Broek et al. 2016). FMRP knockout mice show impaired P_r and short-term plasticity at excitatory synapses (Patel et al. 2013, Wang et al. 2014). At anterior cingulate cortical synapses, preLTP was abolished in FMRP knockout mice (Koga et al. 2015). At hippocampal inhibitory synapses, presynaptic eCB-mediated LTD is increased (Zhang & Alger 2010), whereas in NAc and the prefrontal cortex, eCB-mediated LTD is decreased (Jung et al. 2012). Alterations in the distance between group-I mGluRs and the eCB-producing enzyme diacylglycerol lipase alpha (DGLα) could explain these differences. Nontranslational roles for presynaptic FMRP, such as regulation of ion channels that control action potential waveform (Deng et al. 2013) and Ca^{2+} influx (Ferron et al. 2014), have also been described. Beyond FMRP, another protein for which strong links to autism have been identified is the presynaptically expressed CAM neurexin and its numerous postsynaptic docking proteins (Jang et al. 2017, Südhof 2017). While neurexin can control P_r and therefore alter presynaptic plasticity, more work is needed to establish how transsynaptic signaling is disrupted in autism.

Neurodegenerative Diseases

Patients with Alzheimer, Parkinson, or Huntington disease have toxic protein accumulations in the brain, which can trigger synapse loss, dysfunction, and cell death (Sheng et al. 2012, Waites & Garner 2011). Alzheimer's disease is the most common cause of dementia, with β-amyloid (Aβ) protein plaque and insoluble filamentous microtubule-associated protein tau accumulations frequently observed (Forner et al. 2017, Sheng et al. 2012). Altered Aβ levels abolish presynaptic MF-LTP (Wang et al. 2008, Witton et al. 2010). The Aβ-producing enzyme presenilin is critical for short-term facilitation and LTP at CA3-CA1 synapses (Zhang et al. 2009). Aβ also interferes with eCB-mediated disinhibition and perhaps iLTD, which indirectly prevents LTP (Orr et al. 2014). Presynaptic plasticity of corticostriatal synaptic transmission is important for regulating basal ganglia activity, motor learning, and Parkinson's and Huntington's diseases (Kreitzer & Malenka 2008). Mutations in the Parkinson's disease--linked gene encoding presynaptic α-synuclein results in impaired vesicle mobility and P_r (Cheng et al. 2011). Suppressing α-synuclein blocks preLTP in cultured hippocampal neurons (Liu et al. 2004). In a pharmacological model of the disease, presynaptic plasticity was impaired at corticostriatal synapses (Picconi et al. 2003). The eCB system is an attractive therapeutic target because inhibiting eCB degradation rescued preLTD at corticostriatal synapses and ameliorated motor deficits (Kreitzer & Malenka 2007).

Drugs of Abuse

PreLTP and preLTD are involved in neural adaptations induced by different drugs of abuse (Lüscher & Malenka 2011). Repeated exposure to cocaine in vivo facilitates LTP at excitatory synaptic inputs to dopaminergic ventral tegmental area (VTA) neurons, which is due in part to cocaine-induced eCB release and iLTD (Liu et al. 2005, Pan et al. 2008). Cocaine promotes presynaptic iLTP at interneurons projecting from the NAc to interneurons of the VTA that synapse onto dopaminergic VTA neurons (Bocklisch et al. 2013). These forms of long-term inhibitory plasticity in the VTA ultimately regulate dopaminergic neuron activity to control drug-seeking behavior. In contrast to cocaine, morphine and stress prevented presynaptic iLTP in the VTA and the mechanism involved NO (Nugent et al. 2007) and κ-opioid receptors (Graziane et al. 2013, Polter et al. 2014). Blocking the κ-opioid receptors may be a viable therapeutic target because it restored iLTP and prevented cocaine seeking. Single cocaine exposure and single or chronic THC exposure completely abolished eCB-mediated LTD in the NAc (Fourgeaud et al. 2004, Hoffman et al. 2003, Mato et al. 2004). Presumably this alters reward circuit output in the VTA. Moreover, drugs of abuse can engage compensatory signaling mechanisms to cope with new and unnatural constraints placed on the circuit. For example, chronic THC exposure engages homeostatic mechanisms that produce a mechanistically novel (eCB-independent) form of preLTD that is not observed in naïve brains (Mato et al. 2005). It is likely that many synapses in the brain undergo or attempt to undergo homeostatic compensatory mechanisms because of chronic drug use. The long-term consequences of these molecular changes on behavior warrants further research.

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LITERATURE CITED

Abbott LF, Regehr WG. 2004 Synaptic computation. Nature 431:796–803 [PubMed: 15483601]

Acuna C, Liu X, Gonzalez A, Südhof TC. 2015 RIM-BPs mediate tight coupling of action potentials to Ca^{2+}-triggered neurotransmitter release. Neuron 87:1234–47 [PubMed: 26402606]

Ahmed MS, Siegelbaum SA. 2009 Recruitment of N-type Ca^{2+} channels during LTP enhances low release efficacy of hippocampal CA1 perforant path synapses. Neuron 63:372–85 [PubMed: 19679076]

Akins MR, Berk-Rauch HE, Kwan KY, Mitchell ME, Shepard KA, et al. 2017 Axonal ribosomes and mRNAs associate with fragile X granules in adult rodent and human brains. Hum. Mol. Genet 26:192–209 [PubMed: 28082376]

Alvarez J, Giuditta A, Koenig E. 2000 Protein synthesis in axons and terminals: significance for maintenance, plasticity and regulation of phenotype. With a critique of slow transport theory. Prog. Neurobiol 62:1–62 [PubMed: 10821981]

Anderson GR, Aoto J, Tabuchi K, Foldy C, Covy J, et al. 2015 β-neurexins control neural circuits by regulating synaptic endocannabinoid signaling. Cell 162:593–606 [PubMed: 26213384]

Andrade-Talavera Y, Duque-Feria P, Paulsen O, Rodríguez-Moreno A. 2016 Presynaptic spike timing-dependent long-term depression in the mouse hippocampus. Cereb. Cortex 26:3637–54 [PubMed: 27282393]

Atwood BK, Lovinger DM, Mathur BN. 2014 Presynaptic long-term depression mediated by $G_{i/o}$-coupled receptors. Trends Neurosci. 37:663–73 [PubMed: 25160683]

Atwood HL, Wojtowicz JM. 1999 Silent synapses in neural plasticity: current evidence. Learn. Mem 6:542–71 [PubMed: 10641762]

Azad SC, Monory K, Marsicano G, Cravatt BF, Lutz B, et al. 2004 Circuitry for associative plasticity in the amygdala involves endocannabinoid signaling. J. Neurosci 24:9953–61 [PubMed: 15525780]

Basu J, Srinivas KV, Cheung SK, Taniguchi H, Huang ZJ, Siegelbaum SA. 2013 A corticohippocampal learning rule shapes inhibitory microcircuit activity to enhance hippocampal information flow. Neuron 79: 1208–21 [PubMed: 24050406]

Bauer EP, LeDoux JE. 2004 Heterosynaptic long-term potentiation of inhibitory interneurons in the lateral amygdala. J. Neurosci 24:9507–12 [PubMed: 15509737]

Becker N, Wierenga CJ, Fonseca R, Bonhoeffer T, Nagerl UV. 2008 LTD induction causes morphological changes of presynaptic boutons and reduces their contacts with spines. Neuron 60:590–97 [PubMed: 19038217]

Blundell J, Kaeser PS, Südhof TC, Powell CM. 2010 RIM1α and interacting proteins involved in presynaptic plasticity mediate prepulse inhibition and additional behaviors linked to schizophrenia. J. Neurosci 30:5326–33 [PubMed: 20392954]

Bocklisch C, Pascoli V, Wong JC, House DR, Yvon C, et al. 2013 Cocaine disinhibits dopamine neurons by potentiation of GABA transmission in the ventral tegmental area. Science 341:1521–25 [PubMed: 24072923]

Bolshakov VY, Golan H, Kandel ER, Siegelbaum SA. 1997 Recruitment of new sites of synaptic transmission during the cAMP-dependent late phase of LTP at CA3-CA1 synapses in the hippocampus. Neuron 19:635–51 [PubMed: 9331354]

Bourne JN, Chirillo MA, Harris KM. 2013 Presynaptic ultrastructural plasticity along CA3→CA1 axons during long-term potentiation in mature hippocampus. J. Comp. Neurol 521:3898–912 [PubMed: 23784793]

Broek JAC, Lin Z, de Gruiter HM, van't Spijker H, Haasdijk ED, et al. 2016 Synaptic vesicle dynamic changes in a model of fragile X. Mol. Autism 7:17 [PubMed: 26933487]

Buonanno A 2010 The neuregulin signaling pathway and schizophrenia: from genes to synapses and neural circuits. Brain Res. Bull 83:122–31 [PubMed: 20688137]

Buzsaki G 2010 Neural syntax: cell assemblies, synapsembles, and readers. Neuron 68:362–85 [PubMed: 21040841]

Castillo PE. 2012 Presynaptic LTP and LTD of excitatory and inhibitory synapses. Cold Spring Harb. Perspect. Biol 4:a005728 [PubMed: 22147943]

Castillo PE, Chiu CQ, Carroll RC. 2011 Long-term plasticity at inhibitory synapses. Curr. Opin. Neurobiol 21:328–38 [PubMed: 21334194]

Castillo PE, Younts TJ, Chávez AE, Hashimotodani Y. 2012 Endocannabinoid signaling and synaptic function. Neuron 76:70–81 [PubMed: 23040807]

Chaudhuri R, Fiete I. 2016 Computational principles of memory. Nat. Neurosci 19:394–403 [PubMed: 26906506]

Chavan V, Willis J, Walker SK, Clark HR, Liu X, et al. 2015 Central presynaptic terminals are enriched in ATP but the majority lack mitochondria. PLOS ONE 10:e0125185 [PubMed: 25928229]

Cheng F, Vivacqua G, Yu S. 2011 The role of α-synuclein in neurotransmission and synaptic plasticity. J. Chem. Neuroanat 42:242–48 [PubMed: 21167933]

Cho JH, Deisseroth K, Bolshakov VY. 2013 Synaptic encoding of fear extinction in mPFC-amygdala circuits. Neuron 80:1491–507 [PubMed: 24290204]

Cho RW, Buhl LK, Volfson D, Tran A, Li F, et al. 2015 Phosphorylation of complexin by PKA regulates activity-dependent spontaneous neurotransmitter release and structural synaptic plasticity. Neuron 88:749–61 [PubMed: 26590346]

Christie SB, Akins MR, Schwob JE, Fallon JR. 2009 The FXG: a presynaptic fragile X granule expressed in a subset of developing brain circuits. J. Neurosci 29:1514–24 [PubMed: 19193898]

Cingolani LA, Goda Y. 2008 Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. Nat. Rev. Neurosci 9:344–56 [PubMed: 18425089]

Contractor A, Rogers C, Maron C, Henkemeyer M, Swanson GT, Heinemann SF. 2002 Trans-synaptic Eph receptor-ephrin signaling in hippocampal mossy fiber LTP. Science 296:1864–69 [PubMed: 12052960]

Costa RP, Mizusaki BE, Sjöström PJ, van Rossum MC. 2017 Functional consequences of pre- and postsynaptic expression of synaptic plasticity. Philos. Trans. R. Soc. B 372:20160153

Crabtree GW, Gogos JA. 2014 Synaptic plasticity, neural circuits, and the emerging role of altered short-term information processing in schizophrenia. Front. Synaptic Neurosci 6:28 [PubMed: 25505409]

Crawford DC, Chang CY, Hyrc KL, Mennerick S. 2011 Calcium-independent inhibitory G-protein signaling induces persistent presynaptic muting of hippocampal synapses. J. Neurosci 31:979–91 [PubMed: 21248122]

Crawford DC, Mennerick S. 2012 Presynaptically silent synapses: dormancy and awakening of presynaptic vesicle release. Neuroscientist 18:216–23 [PubMed: 21908849]

Dalva MB, McClelland AC, Kayser MS. 2007 Cell adhesion molecules: signalling functions at the synapse. Nat. Rev. Neurosci 8:206–20 [PubMed: 17299456]

Darnell JC, Klann E. 2013 The translation of translational control by FMRP: therapeutic targets for FXS. Nat. Neurosci 16:1530–36 [PubMed: 23584741]

Davis GW, Müller M. 2015 Homeostatic control of presynaptic neurotransmitter release. Annu. Rev. Physiol 77:251–70 [PubMed: 25386989]

Deguchi Y, Harada M, Shinohara R, Lazarus M, Cherasse Y, et al. 2016 mDia and ROCK mediate actin-dependent presynaptic remodeling regulating synaptic efficacy and anxiety. Cell Rep. 17:2405–17 [PubMed: 27880913]

Deneve S, Alemi A, Bourdoukan R. 2017 The brain as an efficient and robust adaptive learner. Neuron 94:969–77 [PubMed: 28595053]

Deng PY, Rotman Z, Blundon JA, Cho Y, Cui J, et al. 2013 FMRP regulates neurotransmitter release and synaptic information transmission by modulating action potential duration via BK channels. Neuron 77:696–711 [PubMed: 23439122]

Earls LR, Zakharenko SS. 2014 A synaptic function approach to investigating complex psychiatric diseases. Neuroscientist 20:257–71 [PubMed: 23907185]

Eggermann E, Bucurenciu I, Goswami SP, Jonas P. 2011 Nanodomain coupling between Ca^{2+} channels and sensors of exocytosis at fast mammalian synapses. Nat. Rev. Neurosci 13:7–21 [PubMed: 22183436]

Evstratova A, Tóth K. 2014 Information processing and synaptic plasticity at hippocampal mossy fiber terminals. Front. Cell Neurosci. 8:28 [PubMed: 24550783]

Fernandes HB, Riordan S, Nomura T, Remmers CL, Kraniotis S, et al. 2015 Epac2 mediates cAMP-dependent potentiation of neurotransmission in the hippocampus. J. Neurosci 35:6544–53 [PubMed: 25904804]

Fernandez-Busnadiego R, Asano S, Oprisoreanu AM, Sakata E, Doengi M, et al. 2013 Cryo-electron tomography reveals a critical role of RIM1alpha in synaptic vesicle tethering. J Cell Biol 201: 725–40 [PubMed: 23712261]

Ferron L, Nieto-Rostro M, Cassidy JS, Dolphin AC. 2014 Fragile X mental retardation protein controls synaptic vesicle exocytosis by modulating N-type calcium channel density. Nat. Commun 5:3628 [PubMed: 24709664]

Forner S, Baglietto-Vargas D, Martini AC, Trujillo-Estrada L, LaFerla FM. 2017 Synaptic impairment in Alzheimer's disease: a dysregulated symphony. Trends Neurosci. 40:347–57 [PubMed: 28494972]

Fourcaudot E, Gambino F, Casassus G, Poulain B, Humeau Y, Luthi A. 2009 L-type voltage-dependent Ca^{2+} channels mediate expression of presynaptic LTP in amygdala. Nat. Neurosci 12:1093–95 [PubMed: 19648911]

Fourgeaud L, Mato S, Bouchet D, Hemar A, Worley PF, Manzoni OJ. 2004 A single in vivo exposure to cocaine abolishes endocannabinoid-mediated long-term depression in the nucleus accumbens. J. Neurosci 24:6939–45 [PubMed: 15295029]

Frias CP, Wierenga CJ. 2013 Activity-dependent adaptations in inhibitory axons. Front. Cell Neurosci 7:219 [PubMed: 24312009]

Froemke RC. 2015 Plasticity of cortical excitatory-inhibitory balance. Annu. Rev. Neurosci 38:195–219 [PubMed: 25897875]

Froemke RC, Carcea I, Barker AJ, Yuan K, Seybold BA, et al. 2013 Long-term modification of cortical synapses improves sensory perception. Nat. Neurosci 16:79–88 [PubMed: 23178974]

Galimberti I, Gogolla N, Alberi S, Santos AF, Müller D, Caroni P. 2006 Long-term rearrangements of hippocampal mossy fiber terminal connectivity in the adult regulated by experience. Neuron 50:749–63 [PubMed: 16731513]

García-Morales V, Montero F, Moreno-López B. 2015 Cannabinoid agonists rearrange synaptic vesicles at excitatory synapses and depress motoneuron activity in vivo. Neuropharmacology 92:69–79 [PubMed: 25595101]

Gibson JR, Huber KM, Südhof TC. 2009 Neuroligin-2 deletion selectively decreases inhibitory synaptic transmission originating from fast-spiking but not from somatostatin-positive interneurons. J. Neurosci 29:13883–97 [PubMed: 19889999]

Glebov OO, Jackson RE, Winterflood CM, Owen DM, Barker EA, et al. 2017 Nanoscale structural plasticity of the active zone matrix modulates presynaptic function. Cell Rep. 18:2715–28 [PubMed: 28297674]

Gogolla N, Galimberti I, Caroni P. 2007 Structural plasticity of axon terminals in the adult. Curr. Opin. Neurobiol 17:516–24 [PubMed: 17950593]

Gogolla N, Galimberti I, Deguchi Y, Caroni P. 2009 Wnt signaling mediates experience-related regulation of synapse numbers and mossy fiber connectivities in the adult hippocampus. Neuron 62:510–25 [PubMed: 19477153]

Gómez-Gonzalo M, Navarrete M, Perea G, Covelo A, Martín-Fernández M, et al. 2015 Endocannabinoids induce lateral long-term potentiation of transmitter release by stimulation of gliotransmission. Cereb. Cortex 25:3699–712 [PubMed: 25260706]

Graziane NM, Polter AM, Briand LA, Pierce RC, Kauer JA. 2013 Kappa opioid receptors regulate stress-induced cocaine seeking and synaptic plasticity. Neuron 77:942–54 [PubMed: 23473323]

Hagena H, Manahan-Vaughan D. 2011 Learning-facilitated synaptic plasticity at CA3 mossy fiber and commissural-associational synapses reveals different roles in information processing. Cereb. Cortex 21:2442–49 [PubMed: 21493717]

Han Y, Kaeser PS, Südhof TC, Schneggenburger R. 2011 RIM determines Ca^{2+} channel density and vesicle docking at the presynaptic active zone. Neuron 69:304–16 [PubMed: 21262468]

Harris JJ, Jolivet R, Attwell D. 2012 Synaptic energy use and supply. Neuron 75:762–77 [PubMed: 22958818]

Hayashi-Takagi A, Yagishita S, Nakamura M, Shirai F, Wu YI, et al. 2015 Labelling and optical erasure of synaptic memory traces in the motor cortex. Nature 525:333–38 [PubMed: 26352471]

Hebert-Chatelain E, Desprez T, Serrat R, Bellocchio L, Soria-Gomez E, et al. 2016 A cannabinoid link between mitochondria and memory. Nature 539:555–59 [PubMed: 27828947]

Hegde AN. 2017 Proteolysis, synaptic plasticity and memory. Neurobiol. Learn. Mem 138:98–110 [PubMed: 27614141]

Hennequin G, Agnes EJ, Vogels TP. 2017 Inhibitory plasticity: balance, control, and codependence. Annu. Rev. Neurosci 40:557–79 [PubMed: 28598717]

Hoffman AF, Oz M, Caulder T, Lupica CR. 2003 Functional tolerance and blockade of long-term depression at synapses in the nucleus accumbens after chronic cannabinoid exposure. J. Neurosci 23:4815–20 [PubMed: 12832502]

Holtmaat A, Caroni P. 2016 Functional and structural underpinnings of neuronal assembly formation in learning. Nat. Neurosci 19:1553–62 [PubMed: 27749830]

Hsiao K, Harony-Nicolas H, Buxbaum JD, Bozdagi-Gunal O, Benson DL. 2016 Cyfip1 regulates presynaptic activity during development. J. Neurosci 36:1564–76 [PubMed: 26843638]

Huang YY, Kandel ER. 1998 Postsynaptic induction and PKA-dependent expression of LTP in the lateral amygdala. Neuron 21:169–78 [PubMed: 9697861]

Humeau Y, Shaban H, Bissiere S, Luthi A. 2003 Presynaptic induction of heterosynaptic associative plasticity in the mammalian brain. Nature 426:841–45 [PubMed: 14685239]

Jackman SL, Regehr WG. 2017 The mechanisms and functions of synaptic facilitation. Neuron 94:447–64 [PubMed: 28472650]

Jang S, Lee H, Kim E. 2017 Synaptic adhesion molecules and excitatory synaptic transmission. Curr. Opin. Neurobiol 45:45–50 [PubMed: 28390263]

Jedlicka P, Hoon M, Papadopoulos T, Vlachos A, Winkels R, et al. 2011 Increased dentate gyrus excitability in neuroligin-2-deficient mice in vivo. Cereb. Cortex 21:357–67 [PubMed: 20530218]

Jiang X, Litkowski PE, Taylor AA, Lin Y, Snider BJ, Moulder KL. 2010 A role for the ubiquitin-proteasome system in activity-dependent presynaptic silencing. J. Neurosci 30:1798–809 [PubMed: 20130189]

Jones BW, Deem J, Younts TJ, Weisenhaus M, Sanford CA, et al. 2016 Targeted deletion of AKAP7 in dentate granule cells impairs spatial discrimination. eLife 5:e20695 [PubMed: 27911261]

Jourdain P, Bergersen LH, Bhaukaurally K, Bezzi P, Santello M, et al. 2007 Glutamate exocytosis from astrocytes controls synaptic strength. Nat. Neurosci 10:331–39 [PubMed: 17310248]

Jung KM, Sepers M, Henstridge CM, Lassalle O, Neuhofer D, et al. 2012 Uncoupling of the endocannabinoid signalling complex in a mouse model of fragile X syndrome. Nat. Commun 3:1080 [PubMed: 23011134]

Kaeser-Woo YJ, Younts TJ, Yang X, Zhou P, Wu D, et al. 2013 Synaptotagmin-12 phosphorylation by cAMP-dependent protein kinase is essential for hippocampal mossy fiber LTP. J. Neurosci 33:9769–80 [PubMed: 23739973]

Katayama N, Yamamori S, Fukaya M, Kobayashi S, Watanabe M, et al. 2017 SNAP-25 phosphorylation at Ser187 regulates synaptic facilitation and short-term plasticity in an age-dependent manner. Sci. Rep 7:7996 [PubMed: 28801590]

Koga K, Liu MG, Qiu S, Song Q, O'Den G, et al. 2015 Impaired presynaptic long-term potentiation in the anterior cingulate cortex of *Fmr1* knock-out mice. J. Neurosci 35:2033–43 [PubMed: 25653361]

Kreitzer AC, Malenka RC. 2007 Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. Nature 445:643–47 [PubMed: 17287809]

Kreitzer AC, Malenka RC. 2008 Striatal plasticity and basal ganglia circuit function. Neuron 60:543–54 [PubMed: 19038213]

Krueger DD, Tuffy LP, Papadopoulos T, Brose N. 2012 The role of neurexins and neuroligins in the formation, maturation, and function of vertebrate synapses. Curr. Opin. Neurobiol 22:412–22 [PubMed: 22424845]

Kvajo M, McKellar H, Drew LJ, Lepagnol-Bestel AM, Xiao L, et al. 2011 Altered axonal targeting and short-term plasticity in the hippocampus of Disc1 mutant mice. PNAS 108:E1349–58 [PubMed: 22049344]

Larsen RS, Sjöström PJ. 2015 Synapse-type-specific plasticity in local circuits. Curr. Opin. Neurobiol 35:127–35 [PubMed: 26310110]

Li H, Penzo MA, Taniguchi H, Kopec CD, Huang ZJ, Li B. 2013 Experience-dependent modification of a central amygdala fear circuit. Nat. Neurosci 16:332–39 [PubMed: 23354330]

Lisman JE. 1997 Bursts as a unit of neural information: making unreliable synapses reliable. Trends Neurosci. 20:38–43 [PubMed: 9004418]

Liu QS, Pu L, Poo MM. 2005 Repeated cocaine exposure in vivo facilitates LTP induction in midbrain dopamine neurons. Nature 437:1027–31 [PubMed: 16222299]

Liu S, Ninan I, Antonova I, Battaglia F, Trinchese F, et al. 2004 α-Synuclein produces a long-lasting increase in neurotransmitter release. EMBO J. 23:4506–16 [PubMed: 15510220]

Losonczy A, Biro AA, Nusser Z. 2004 Persistently active cannabinoid receptors mute a subpopulation of hippocampal interneurons. PNAS 101:1362–67 [PubMed: 14734812]

Lu Y, Sun XD, Hou FQ, Bi LL, Yin DM, et al. 2014 Maintenance of GABAergic activity by neuregulin 1-ErbB4 in amygdala for fear memory. Neuron 84:835–46 [PubMed: 25451196]

Lüscher C, Malenka RC. 2011 Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. Neuron 69:650–63 [PubMed: 21338877]

Lutz B 2007 The endocannabinoid system and extinction learning. Mol. Neurobiol 36:92–101 [PubMed: 17952654]

Ma L, Zablow L, Kandel ER, Siegelbaum SA. 1999 Cyclic AMP induces functional presynaptic boutons in hippocampal CA3-CA1 neuronal cultures. Nat. Neurosci 2:24–30 [PubMed: 10195176]

Markram H, Tsodyks M. 1996 Redistribution of synaptic efficacy between neocortical pyramidal neurons. Nature 382:807–10 [PubMed: 8752273]

Maruo T, Mandai K, Takai Y, Mori M. 2016 Activity-dependent alteration of the morphology of a hippocampal giant synapse. Mol. Cell Neurosci 71:25–33 [PubMed: 26687760]

Mato S, Chevaleyre V, Robbe D, Pazos A, Castillo PE, Manzoni OJ. 2004 A single in-vivo exposure to Δ9THC blocks endocannabinoid-mediated synaptic plasticity. Nat. Neurosci 7:585–86 [PubMed: 15146190]

Mato S, Lafourcade M, Robbe D, Bakiri Y, Manzoni OJ. 2008 Role of the cyclic-AMP/PKA cascade and of P/Q-type Ca^{2+} channels in endocannabinoid-mediated long-term depression in the nucleus accumbens. Neuropharmacology 54:87–94 [PubMed: 17606273]

Mato S, Robbe D, Puente N, Grandes P, Manzoni OJ. 2005 Presynaptic homeostatic plasticity rescues long-term depression after chronic Δ^9-tetrahydrocannabinol exposure. J. Neurosci 25:11619–27 [PubMed: 16354920]

McKernan MG, Shinnick-Gallagher P. 1997 Fear conditioning induces a lasting potentiation of synaptic currents in vitro. Nature 390:607–11 [PubMed: 9403689]

Meyer D, Bonhoeffer T, Scheuss V. 2014 Balance and stability of synaptic structures during synaptic plasticity. Neuron 82:430–43 [PubMed: 24742464]

Michel K, Müller JA, Oprisoreanu AM, Schoch S. 2015 The presynaptic active zone: a dynamic scaffold that regulates synaptic efficacy. Exp. Cell Res 335:157–64 [PubMed: 25720549]

Min R, Nevian T. 2012 Astrocyte signaling controls spike timing-dependent depression at neocortical synapses. Nat. Neurosci 15:746–53 [PubMed: 22446881]

Min R, Santello M, Nevian T. 2012 The computational power of astrocyte mediated synaptic plasticity. Front. Comput. Neurosci 6:93 [PubMed: 23125832]

Missler M, Zhang W, Rohlmann A, Kattenstroth G, Hammer RE, et al. 2003 α-Neurexins couple Ca^{2+} channels to synaptic vesicle exocytosis. Nature 423:939–48 [PubMed: 12827191]

Monday HR, Castillo PE. 2017 Closing the gap: long-term presynaptic plasticity in brain function and disease. Curr. Opin. Neurobiol 45:106–12 [PubMed: 28570863]

Moulder KL, Jiang X, Chang C, Taylor AA, Benz AM, et al. 2008 A specific role for Ca^{2+}-dependent adenylyl cyclases in recovery from adaptive presynaptic silencing. J. Neurosci 28:5159–68 [PubMed: 18480272]

Moulder KL, Meeks JP, Shute AA, Hamilton CK, de Erausquin G, Mennerick S. 2004 Plastic elimination of functional glutamate release sites by depolarization. Neuron 42:423–35 [PubMed: 15134639]

Mukai J, Tamura M, Fenelon K, Rosen AM, Spellman TJ, et al. 2015 Molecular substrates of altered axonal growth and brain connectivity in a mouse model of schizophrenia. Neuron 86:680–95 [PubMed: 25913858]

Nakamura Y, Harada H, Kamasawa N, Matsui K, Rothman JS, et al. 2015 Nanoscale distribution of presynaptic Ca^{2+} channels and its impact on vesicular release during development. Neuron, 85(1), pp.145–158. [PubMed: 25533484]

Nugent FS, Penick EC, Kauer JA. 2007 Opioids block long-term potentiation of inhibitory synapses. Nature 446:1086–90 [PubMed: 17460674]

Orr AL, Hanson JE, Li D, Klotz A, Wright S, et al. 2014 β-Amyloid inhibits E-S potentiation through suppression of cannabinoid receptor 1-dependent synaptic disinhibition. Neuron 82:1334–45 [PubMed: 24945775]

Pan B, Hillard CJ, Liu QS. 2008 Endocannabinoid signaling mediates cocaine-induced inhibitory synaptic plasticity in midbrain dopamine neurons. J. Neurosci 28:1385–97 [PubMed: 18256258]

Patel AB, Hays SA, Bureau I, Huber KM, Gibson JR. 2013 A target cell-specific role for presynaptic *Fmr1* in regulating glutamate release onto neocortical fast-spiking inhibitory neurons. J. Neurosci 33:2593–604 [PubMed: 23392687]

Pathak D, Shields LY, Mendelsohn BA, Haddad D, Lin W, et al. 2015 The role of mitochondrially derived ATP in synaptic vesicle recycling. J. Biol. Chem 290:22325–36 [PubMed: 26126824]

Pelkey KA, Topolnik L, Lacaille JC, McBain CJ. 2006 Compartmentalized Ca^{2+} channel regulation at divergent mossy-fiber release sites underlies target cell-dependent plasticity. Neuron 52:497–510 [PubMed: 17088215]

Perea G, Araque A. 2007 Astrocytes potentiate transmitter release at single hippocampal synapses. Science 317:1083–86 [PubMed: 17717185]

Perea G, Navarrete M, Araque A. 2009 Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci. 32:421–31 [PubMed: 19615761]

Petzoldt AG, Lutzkendorf J, Sigrist SJ. 2016 Mechanisms controlling assembly and plasticity of presynaptic active zone scaffolds. Curr. Opin. Neurobiol 39:69–76 [PubMed: 27131423]

Picconi B, Centonze D, Hakansson K, Bernardi G, Greengard P, et al. 2003 Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. Nat. Neurosci 6:501–6 [PubMed: 12665799]

Pilo Boyl P, Di Nardo A, Mulle C, Sassoè-Pognetto M, Panzanelli P, et al. 2007 Profilin2 contributes to synaptic vesicle exocytosis, neuronal excitability, and novelty-seeking behavior. EMBO J. 26:2991–3002 [PubMed: 17541406]

Piskorowski RA, Nasrallah K, Diamantopoulou A, Mukai J, Hassan SI, et al. 2016 Age-dependent specific changes in area CA2 of the hippocampus and social memory deficit in a mouse model of the 22q11.2 deletion syndrome. Neuron 89:163–76 [PubMed: 26748091]

Polter AM, Bishop RA, Briand LA, Graziane NM, Pierce RC, Kauer JA. 2014 Poststress block of κ opioid receptors rescues long-term potentiation of inhibitory synapses and prevents reinstatement of cocaine seeking. Biol. Psychiatry 76:785–93 [PubMed: 24957331]

Poo MM, Pignatelli M, Ryan TJ, Tonegawa S, Bonhoeffer T, et al. 2016 What is memory? The present state of the engram. BMC Biol. 14:40 [PubMed: 27197636]

Powell CM, Schoch S, Monteggia L, Barrot M, Matos MF, et al. 2004 The presynaptic active zone protein RIM1α is critical for normal learning and memory. Neuron 42:143–53 [PubMed: 15066271]

Ramírez-Franco J, Bartolomé-Martin D, Alonso B, Torres M, Sánchez-Prieto J. 2014 Cannabinoid type 1 receptors transiently silence glutamatergic nerve terminals of cultured cerebellar granule cells. PLOS ONE 9:e88594 [PubMed: 24533119]

Rangaraju V, Calloway N, Ryan TA. 2014 Activity-driven local ATP synthesis is required for synaptic function. Cell 156:825–35 [PubMed: 24529383]

Rebola N, Carta M, Mulle C. 2017 Operation and plasticity of hippocampal CA3 circuits: implications for memory encoding. Nat. Rev. Neurosci 18:208–20 [PubMed: 28251990]

Regehr WG. 2012 Short-term presynaptic plasticity. Cold Spring Harb. Perspect. Biol 4:a005702 [PubMed: 22751149]

Robbe D, Kopf M, Remaury A, Bockaert J, Manzoni OJ. 2002 Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens. PNAS 99:8384–88 [PubMed: 12060781]

Rost BR, Schneider F, Grauel MK, Wozny C, Bentz C, et al. 2015 Optogenetic acidification of synaptic vesicles and lysosomes. Nat. Neurosci 18:1845–52 [PubMed: 26551543]

Ruediger S, Vittori C, Bednarek E, Genoud C, Strata P, et al. 2011 Learning-related feedforward inhibitory connectivity growth required for memory precision. Nature 473:514–18 [PubMed: 21532590]

Sankaranarayanan S, Atluri PP, Ryan TA. 2003 Actin has a molecular scaffolding, not propulsive, role in presynaptic function. Nat. Neurosci 6:127–35 [PubMed: 12536209]

Schmitz SK, King C, Kortleven C, Huson V, Kroon T, et al. 2016 Presynaptic inhibition upon CB1 or mGlu2/3 receptor activation requires ERK/MAPK phosphorylation of Munc18–1. EMBO J. 35:1236–50 [PubMed: 27056679]

Schuemann A, Klawiter A, Bonhoeffer T, Wierenga CJ. 2013 Structural plasticity of GABAergic axons is regulated by network activity and $GABA_A$ receptor activation. Front. Neural Circuits 7:113 [PubMed: 23805077]

Seshadri S, Faust T, Ishizuka K, Delevich K, Chung Y, et al. 2015 Interneuronal DISC1 regulates NRG1-ErbB4 signalling and excitatory-inhibitory synapse formation in the mature cortex. Nat. Commun 6:10118 [PubMed: 26656849]

Shaban H, Humeau Y, Herry C, Cassasus G, Shigemoto R, et al. 2006 Generalization of amygdala LTP and conditioned fear in the absence of presynaptic inhibition. Nat. Neurosci 9:1028–35 [PubMed: 16819521]

Shamir A, Kwon OB, Karavanova I, Vullhorst D, Leiva-Salcedo E, et al. 2012 The importance of the NRG-1/ErbB4 pathway for synaptic plasticity and behaviors associated with psychiatric disorders. J. Neurosci 32:2988–97 [PubMed: 22378872]

Sheffler-Collins SI, Dalva MB. 2012 EphBs: an integral link between synaptic function and synaptopathies. Trends Neurosci. 35:293–304 [PubMed: 22516618]

Sheng M, Sabatini BL, Südhof TC. 2012 Synapses and Alzheimer's disease. Cold Spring Harb. Perspect. Biol 4:a005777 [PubMed: 22491782]

Shigeoka T, Jung H, Jung J, Turner-Bridger B, Ohk J, et al. 2016 Dynamic axonal translation in developing and mature visual circuits. Cell 166:181–92 [PubMed: 27321671]

Shin RM, Tully K, Li Y, Cho JH, Higuchi M, et al. 2010 Hierarchical order of coexisting pre- and postsynaptic forms of long-term potentiation at synapses in amygdala. PNAS 107:19073–78 [PubMed: 20956319]

Siegert S, Seo J, Kwon EJ, Rudenko A, Cho S, et al. 2015 The schizophrenia risk gene product miR-137 alters presynaptic plasticity. Nat. Neurosci 18:1008–16 [PubMed: 26005852]

Sigrist SJ, Schmitz D. 2011 Structural and functional plasticity of the cytoplasmic active zone. Curr. Opin. Neurobiol 21:144–50 [PubMed: 20832284]

Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA. 2010 Impaired hippocampalprefrontal synchrony in a genetic mouse model of schizophrenia. Nature 464:763–67 [PubMed: 20360742]

Sinnen BL, Bowen AB, Forte JS, Hiester BG, Crosby KC, et al. 2017 Optogenetic control of synaptic composition and function. Neuron 93:646–60.e5 [PubMed: 28132827]

Sjöström PJ, Turrigiano GG, Nelson SB. 2003 Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors. Neuron 39:641–54 [PubMed: 12925278]

Smith HL, Bourne JN, Cao G, Chirillo MA, Ostroff LE, et al. 2016 Mitochondrial support of persistent presynaptic vesicle mobilization with age-dependent synaptic growth after LTP. eLife 5:e15275 [PubMed: 27991850]

Spacek J, Harris K, Fiala J. (2004). Atlas of Ultrastructural Neurocytology. Retrieved February 20, 2018, from http://synapseweb.clm.utexas.edu/atlas

Su B, Ji YS, Sun XL, Liu XH, Chen ZY. 2014 Brain-derived neurotrophic factor (BDNF)-induced mitochondrial motility arrest and presynaptic docking contribute to BDNF-enhanced synaptic transmission. J. Biol. Chem 289:1213–26 [PubMed: 24302729]

Südhof TC. 2017 Synaptic Neurexin Complexes: A Molecular Code for the Logic of Neural Circuits. Cell. 171(4), pp.745–769. [PubMed: 29100073]

Sun T, Qiao H, Pan PY, Chen Y, Sheng ZH. 2013 Motile axonal mitochondria contribute to the variability of presynaptic strength. Cell Rep. 4:413–19 [PubMed: 23891000]

Takamori S, Holt M, Stenius K, Lemke EA, Gronborg M, et al. 2006 Molecular anatomy of a trafficking organelle. Cell 127: 831–46 [PubMed: 17110340]

Tang AH, Chen H, Li TP, Metzbower SR, MacGillavry HD, Blanpied TA. 2016 A trans-synaptic nanocolumn aligns neurotransmitter release to receptors. Nature 536:210–14 [PubMed: 27462810]

Tovote P, Fadok JP, Luthi A. 2015 Neuronal circuits for fear and anxiety. Nat. Rev. Neurosci 16:317–31 [PubMed: 25991441]

Turrigiano G 2012 Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harb. Perspect. Biol 4:a005736 [PubMed: 22086977]

Varoqueaux F, Jamain S, Brose N. 2004 Neuroligin 2 is exclusively localized to inhibitory synapses. Eur. J. Cell Biol 83:449–56 [PubMed: 15540461]

Villa KL, Berry KP, Subramanian J, Cha JW, Oh WC, et al. 2016 Inhibitory synapses are repeatedly assembled and removed at persistent sites in vivo. Neuron 89:756–69 [PubMed: 26853302]

Volk L, Chiu SL, Sharma K, Huganir RL. 2015 Glutamate synapses in human cognitive disorders. Annu. Rev. Neurosci 38:127–49 [PubMed: 25897873]

Voronin LL, Cherubini E. 2004 'Deaf, mute and whispering' silent synapses: their role in synaptic plasticity. J. Physiol 557:3–12 [PubMed: 15034124]

Waites CL, Garner CC. 2011 Presynaptic function in health and disease. Trends Neurosci. 34:326–37 [PubMed: 21596448]

Wang H, Song L, Laird F, Wong PC, Lee HK. 2008 BACE1 knock-outs display deficits in activity-dependent potentiation of synaptic transmission at mossy fiber to CA3 synapses in the hippocampus. J. Neurosci 28:8677–81 [PubMed: 18753368]

Wang W, Jia Y, Pham DT, Palmer LC, Jung KM, et al. 2017 Atypical endocannabinoid signaling initiates a new form of memory-related plasticity at a cortical input to hippocampus. Cereb. Cortex 17:1–14

Wang XS, Peng CZ, Cai WJ, Xia J, Jin D, et al. 2014 Activity-dependent regulation of release probability at excitatory hippocampal synapses: a crucial role of fragile X mental retardation protein in neurotransmission. Eur. J. Neurosci 39:1602–12 [PubMed: 24646437]

Wang YC, Lauwers E, Verstreken P. 2017 Presynaptic protein homeostasis and neuronal function. Curr. Opin. Genet. Dev 44:38–46 [PubMed: 28213157]

Wierenga CJ, Becker N, Bonhoeffer T. 2008 GABAergic synapses are formed without the involvement of dendritic protrusions. Nat Neurosci 11: 1044–52 [PubMed: 19160502]

Wilhelm BG, Mandad S, Truckenbrodt S, Krohnert K, Schäfer C et al. 2014 Composition of isolated synaptic boutons reveals the amounts of vesicle trafficking proteins. Science 344: 1023–8 [PubMed: 24876496]

Witton J, Brown JT, Jones MW, Randall AD. 2010 Altered synaptic plasticity in the mossy fibre pathway of transgenic mice expressing mutant amyloid precursor protein. Mol. Brain 3:32 [PubMed: 21040543]

Woo RS, Li XM, Tao Y, Carpenter-Hyland E, Huang YZ, et al. 2007 Neuregulin-1 enhances depolarization-induced GABA release. Neuron 54:599–610 [PubMed: 17521572]

Woodin MA, Maffei AE. 2010 Inhibitory Synaptic Plasticity. New York: Springer

Wu XS, Lee SH, Sheng J, Zhang Z, Zhao WD, et al. 2016 Actin is crucial for all kinetically distinguishable forms of endocytosis at synapses. Neuron 92:1020–35 [PubMed: 27840001]

Yang Y, Calakos N. 2013 Presynaptic long-term plasticity. Front Synaptic Neurosci 5: 8 [PubMed: 24146648]

Yao J, Qi J, Chen G. 2006 Actin-dependent activation of presynaptic silent synapses contributes to long-term synaptic plasticity in developing hippocampal neurons. J. Neurosci 26:8137–47 [PubMed: 16885227]

Younts TJ, Chevaleyre V, Castillo PE. 2013 CA1 pyramidal cell theta-burst firing triggers endocannabinoid-mediated long-term depression at both somatic and dendritic inhibitory synapses. J. Neurosci 33:13743–57 [PubMed: 23966696]

Younts TJ, Monday HR, Dudok B, Klein ME, Jordan BA, et al. 2016 Presynaptic protein synthesis is required for long-term plasticity of GABA release. Neuron 92:479–92 [PubMed: 27764673]

Zhang C, Wu B, Beglopoulos V, Wines-Samuelson M, Zhang D, et al. 2009 Presenilins are essential for regulating neurotransmitter release. Nature 460:632–36 [PubMed: 19641596]

Zhang L, Alger BE. 2010 Enhanced endocannabinoid signaling elevates neuronal excitability in fragile X syndrome. J. Neurosci 30:5724–29 [PubMed: 20410124]

SUMMARY POINTS

1. Long-term, activity-dependent increases and decreases in neurotransmitter release (preLTP and preLTD, respectively) are forms of synaptic plasticity widely expressed in the CNS that can occur at excitatory and inhibitory synapses.
2. Induction typically involves transient increases of presynaptic Ca^{2+}, activation of presynaptic receptors, and retrograde or transsynaptic signaling. Molecules involved in basal neurotransmitter release or short-term plasticity may indirectly have a role in long-term plasticity (e.g., by controlling its induction).
3. Like dendritic spines, axons and presynaptic terminals undergo long-term experience and activity-dependent structural plasticity that are likely associated with changes in synaptic strength. Presynaptic structural plasticity may involve nanoscale changes in protein distribution at the AZ or macroscale changes such as the loss or addition of entire boutons.
4. New evidence supports a role for presynaptic protein synthesis in preLTP and preLTD in the mature brain. Such local protein synthesis could allow rapid response to local cues and help maintain input specificity of plasticity, but whether this is a widespread mechanism of preLTP and preLTD in the brain needs to be determined.
5. Emerging research suggests that long-term plasticity involves coordination between presynaptic and postsynaptic compartments. The mechanisms may include anterograde and retrograde messengers, transsynaptic CAMs, and glia.
6. Computationally, preLTP and preLTD can enhance circuit flexibility by altering short-term synaptic filtering dynamics and introducing correlations or decorrelations in postsynaptic activity.
7. New tools are needed to elucidate the function of presynaptic plasticity in behavior. The development of synapse-specific, light-sensitive or chemical-sensitive modulators of P_r would help resolve this issue.

FUTURE ISSUES

1. Although several molecular targets have been identified, how exactly neurotransmitter release is changed in a long-term manner during preLTP and preLTD remains largely elusive. It is also uncertain whether preLTP or preLTD relies on specific plasticity proteins.
2. Given the high energy cost of maintaining release-competent presynaptic terminals, long term activity-dependent regulation of ATP availability may be a potent and efficient mechanism of controlling presynaptic strength in the long-term, but this idea has not yet been explored.
3. Owing mainly to a lack of selective manipulations that interfere or mimic plasticity in vivo, the precise contribution of preLTP and preLTD to behavior is mostly unknown.
4. Brain function relies on diverse forms of plasticity. How preLTP and preLTD interact in vivo with other plasticities (e.g., Hebbian, nonsynaptic or intrinsic, or homeostatic) is an open question.
5. The stability of memory in the face of molecular turnover is remarkable. How do synapses stably store information while maintaining their plastic capacity?
6. Presynaptic plasticity is clearly impaired in many brain diseases, but whether it is the cause or consequence of the disease is still unknown in most cases.

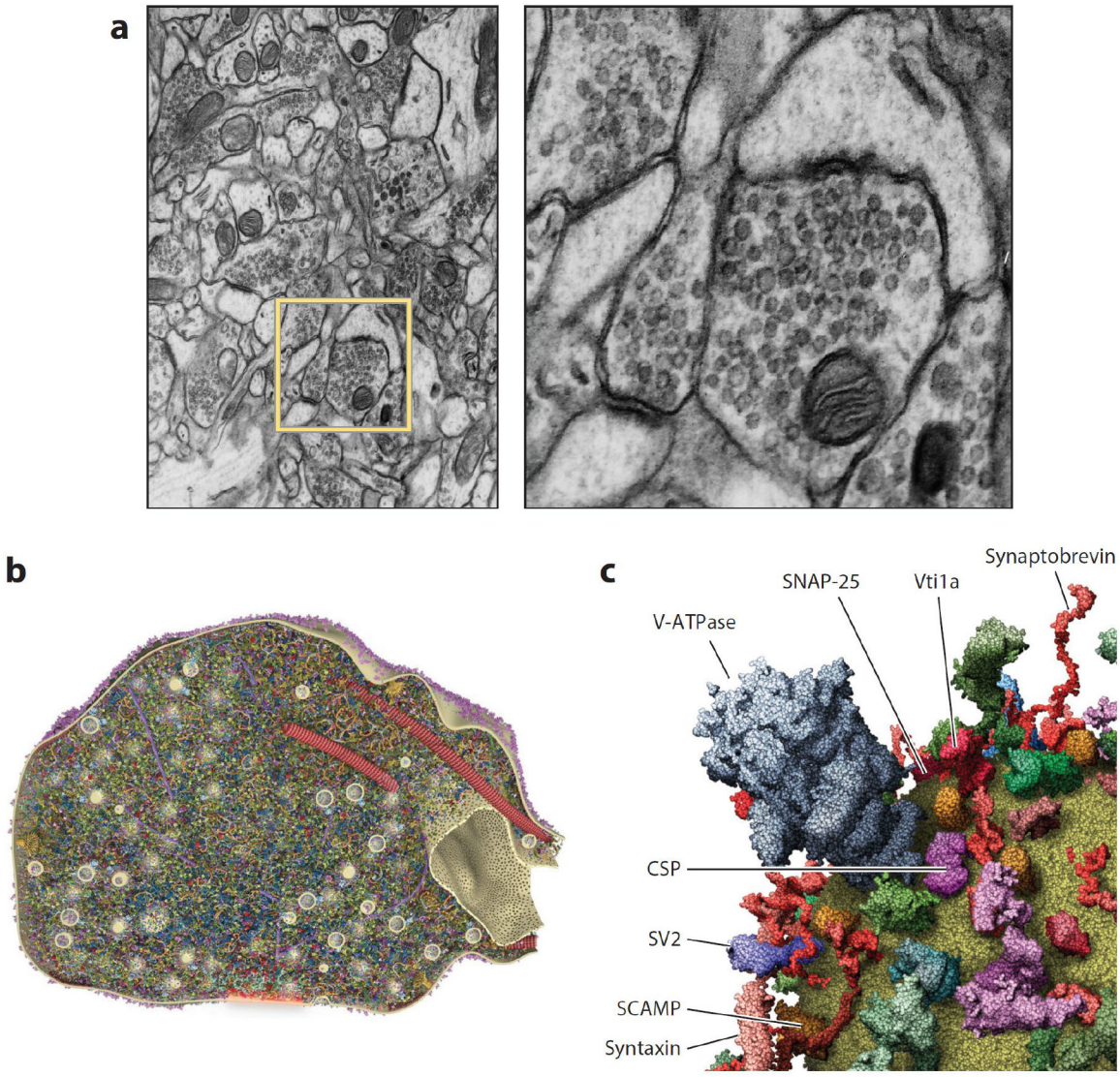

Figure 1.

Presynaptic terminals are complex structures. (*a*) Transmission electron micrograph taken from rat hippocampal neuropil highlighting presynaptic terminals. The right panel is a close-up view of the yellow box in the left panel. Modified from Atlas of Ultrastructural Neurocytology on Synapse Web by Josef Spacek, Kristen Harris, and John Fiala. http://synapseweb.clm.utexas.edu/atlas. (*b*) Quantitative three-dimensional model of a section through an average presynaptic terminal displaying >300,000 proteins in atomic detail. The active zone is shaded red at bottom. From Wilhelm et al. (2014). (*c*) Three-dimensional model of a prototypical synaptic vesicle (close up) containing dozens of proteins in stoichiometrically accurate atomic detail. From Takamori et al. (2006).

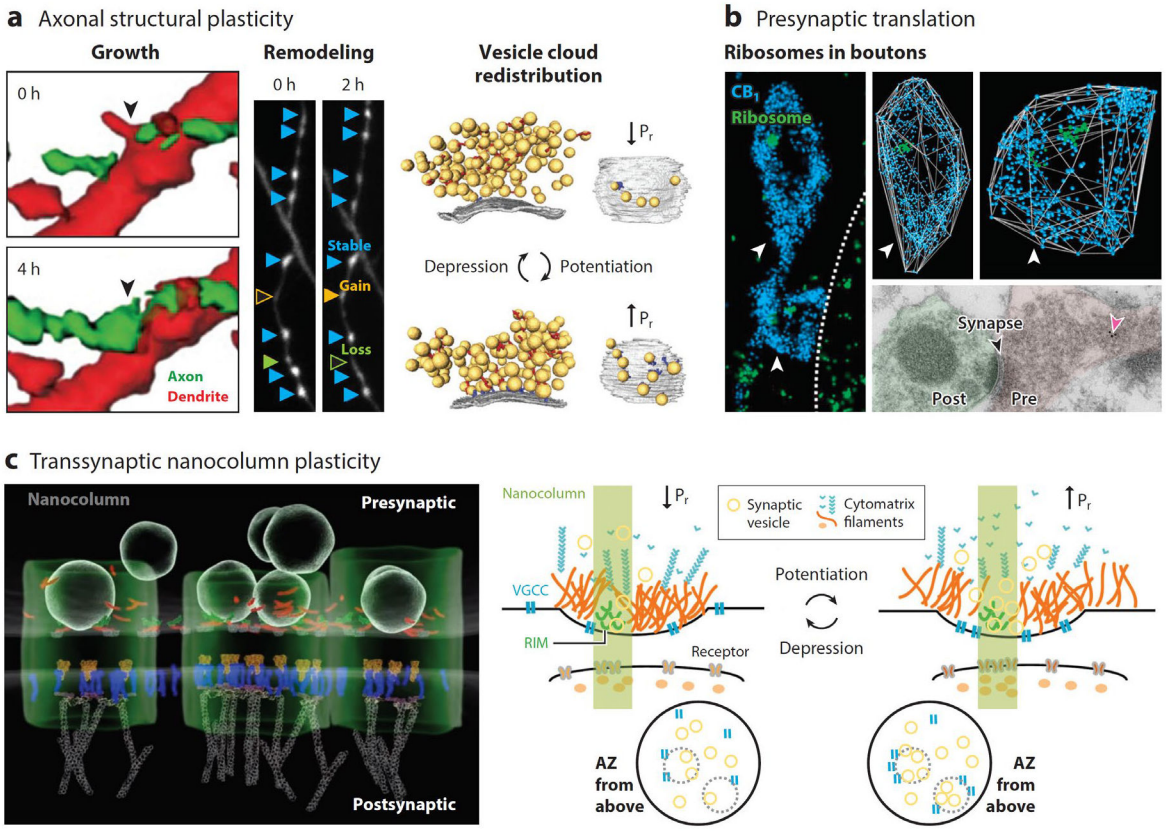

Figure 2.

Emerging molecular mechanisms of presynaptic plasticity. (*a*) Different forms of axonal structural plasticity. (*Left*) Growth: Inhibitory axon (*green*) form a contact on a hippocampal pyramidal cell dendrite (*red*). Arrow indicates the location of a future bouton. Modified from Wierenga et al. (2008). (*Middle*) Remodeling: GABAergic boutons can be stable (*light-blue arrowheads*), gained (*yellow arrowheads*), or lost (*orange arrowheads*). Modified from Schuemann et al. (2013). Images collected from organotypic hippocampal slice cultures using time-lapse, two-photon microscopy. (*Right*) Vesicle cloud redistribution: Synaptic vesicle (*yellow*) number, density, proximity to, and priming or docking state at the AZ(*gray*) can contribute to P_r. Cytomatrix filaments (*red* and *blue*) may also help regulate P_r. Modified from Fernández-Busnadiego et al. (2013). Data collected from cerebrocortical synaptosomes by way of cryo-electron microscopy. (*b*) Ribosomes in presynaptic boutons. (*Left and top-right*) Dual-STORM imaging of CB_1 receptors delineating two GABAergic boutons (*blue*) and 5.8S ribosomal rRNA (*green*) in acute hippocampal slices. Three-dimensional (3D) reconstructed boutons shown at right. Arrowheads indicate the two boutons. Dotted line in left panel outlines CA1 pyramidal cell soma. From Younts et al. (2016). (*Bottom-right*) presynaptic ribosomes (*pink arrow*) revealed by immunogold electron microscopy on retinal ganglion cell axon in the superior colliculus. Modified from Shigeoka et al. (2016). (*c*) (*Left*) Model of synaptic nanocolumn based on data collected by 3D-STORM revealing alignment of presynaptic and postsynaptic molecules. Shown presynaptically are synaptic vesicles, AZ proteins RIM1/2 (*red*) and Munc13 (*green*). Shown postsynaptically are glutamate receptors (*orange*), PSD-95 (*blue*), and actin (*gray*). The green tube highlights the

nanocolumn. Modified from Tang et al. (2016). (*Right*) Schematic representation of the nanocolumn and its modulation. Plasticity can result from changes in presynaptic vesicle or cytomatrix filament clustering or changes in the density or proximity of VGCCs to the active zone. Adapted from Glebov et al. (2017). Abbreviations: AZ, active zone; P_r, probability of release; PSD, postsynaptic density; RIM, Rab-interacting proteins; STORM, Stochastic optical reconstruction microscopy; VGCC, voltage-gated Ca^{2+} channel.

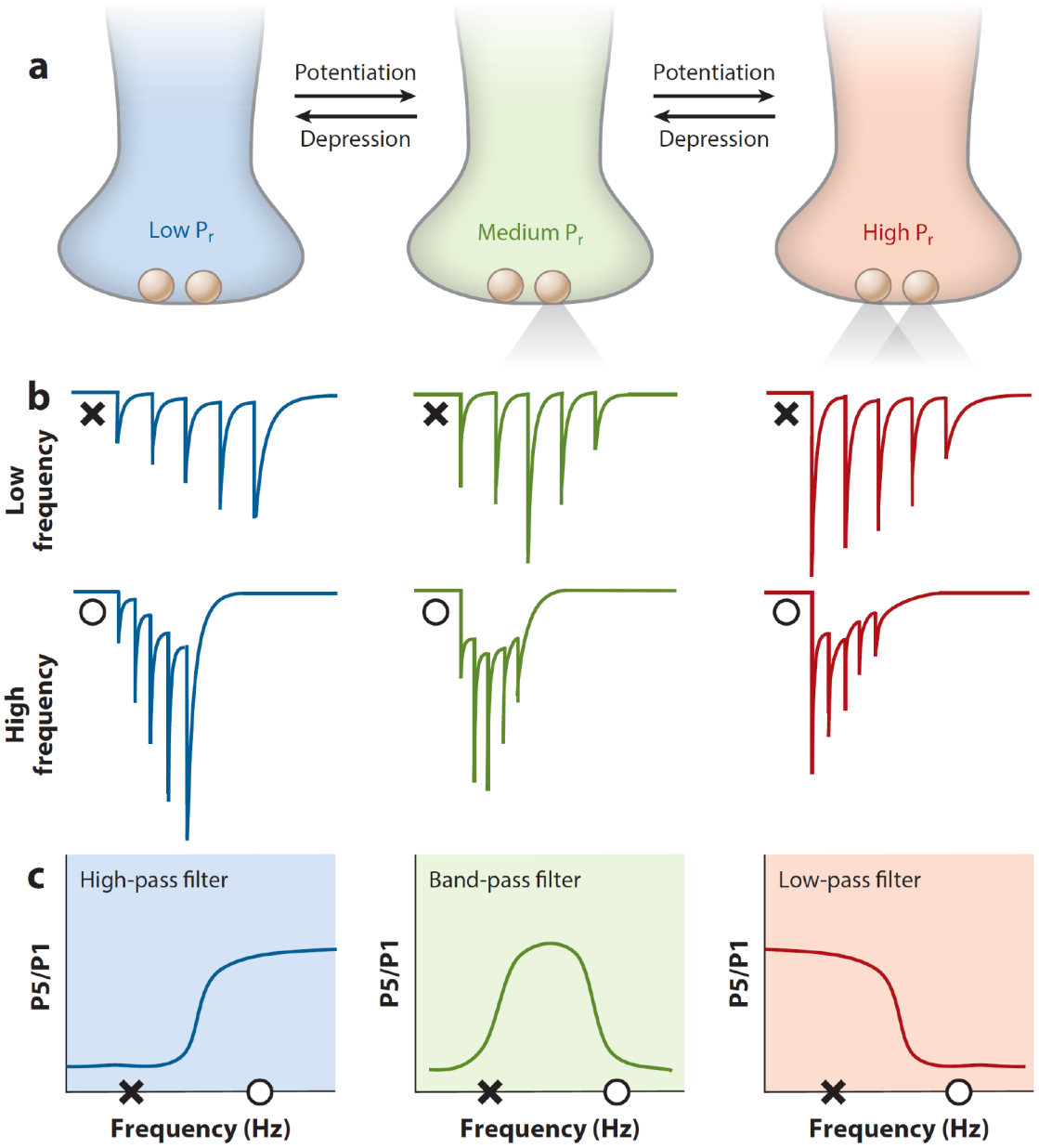

Figure 3.

Long-term presynaptic plasticity modifies short-term plasticity and synaptic filtering. (*a*) PreLTP and preLTD can shift P_r of individual terminals between low, medium, and high modes. (*b*) Schematic EPSCs resulting from five input pulses at relatively low and high frequencies across each P_r. (*c*) Schematic depicting synaptic filtering of excitation across each P_r. Low-, medium-, and high-P_r synapses can respectively exhibit high-pass, band-pass, and low-pass filtering. The amplitude ratio of P5 to P1 as a function of input frequency is shown. X indicates low frequency. O indicates high frequency. Long-term presynaptic plasticity can shift the range and type of filtering at a given synapse. Abbreviations: EPSC,

excitatory postsynaptic current; P5/P1, pulse 5/pulse 1; P_r, release probability; preLTD, presynaptic long-term depression; preLTP, presynaptic long-term potentiation.