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Closing the gap: long-term presynaptic plasticity in brain function and disease

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Abstract

Synaptic plasticity is critical for experience-dependent adjustments of brain function. While most research has focused on the mechanisms that underlie postsynaptic forms of plasticity, comparatively little is known about how neurotransmitter release is altered in a long-term manner. Emerging research suggests that many of the features of canonical “postsynaptic” plasticity, such as associativity, structural changes and bidirectionality, also characterize long-term presynaptic plasticity. Research over the past few years has demonstrated that presynaptic plasticity is a potent regulator of circuit output and function. Moreover, aberrant presynaptic plasticity is a convergent factor of synaptopathies like schizophrenia, addiction, and Autism Spectrum Disorders, and may be a potential target for treatment.

Introduction

Long-term changes in synaptic strength, such as LTP and LTD are believed to critically underlie experience-induced neural adaptations in the brain [1]. These forms of synaptic plasticity typically occur in the time scale of hours and can be expressed postsynaptically as a change in postsynaptic receptor number or function, or presynaptically as a change in neurotransmitter release. While the mechanisms that govern postsynaptic plasticity have been well-characterized, how presynaptic changes emerge is poorly understood. Presynaptic plasticity is an efficient mechanism to change the strength of both excitatory and inhibitory synaptic connections and, thereby, robustly control circuit function and behavior [2, 3]. Pre- and postsynaptic mechanisms of plasticity expand the dynamic range and repertoire by which neurons encode information. Emerging evidence suggests that pre- and postsynaptically expressed plasticity share common properties, and that, regardless of the loci of expression, plastic changes are reciprocally coordinated across the synapse. Here, we summarize recent advances on long-term presynaptic plasticity, assess the mechanistic

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similarities of pre- and postsynaptic plasticity, and examine the increasing evidence that long-term presynaptic plasticity has direct physiological consequences. Finally, we briefly discuss how dysregulation of presynaptic plasticity may contribute to brain disorders.

Induction and expression mechanisms

The induction mechanisms of presynaptic plasticity are diverse and may involve repetitive activity of the presynaptic cell alone, a retrograde messenger released from the postsynaptic cell, or some signal arising from neighboring synapses or astrocytes (for a thorough discussion, see [2, 3]). Typically, activation of a ligand-gated presynaptic receptor or presynaptic calcium influx via voltage-gated calcium channels (VGCCs) triggers a downstream signaling cascade involving kinases and phosphatases. One well-characterized mechanism involves presynaptic cAMP and PKA signaling. Activation of cAMP induces presynaptic LTP at the hippocampal mossy fiber to CA3 pyramidal cell (MF-CA3) synapse and at many other synapses throughout the brain [2]. In contrast, presynaptic inhibition of the cAMP pathway via $G_{i/o}$ coupled receptors, like the cannabinoid-1 receptor (CB_1R), μ -opioid receptor (MOR), dopamine-2 receptor (D_2R), results in presynaptic LTD, which is also a widespread phenomenon [4]. Remarkably, when presynaptic activity alone is sufficient for induction, all synaptic contacts established by the presynaptic neuron are expected to undergo long-term changes in transmitter release. This is in clear contrast to Hebbian rules of synaptic plasticity where coincident presynaptic and postsynaptic activity is required for postsynaptic forms of LTP/LTD.

The precise process by which neurotransmitter release is altered in a long-lasting manner remains largely unknown. This is likely due to the difficulty associated with visualizing and manipulating the axon and minute presynaptic terminals. In addition, neurotransmission is a particularly complex phenomenon that involves multiple steps and molecular players. A number of these steps have been implicated in presynaptic plasticity, including changes in presynaptic calcium influx through VGCCs, and alterations of the release machinery (for a thorough review on these mechanisms, see [2, 3]).

Presynaptic and Postsynaptic plasticity: Common threads?

Growing evidence indicates that general principles of classical postsynaptic N-methyl D-aspartate receptor (NMDAR)-dependent Hebbian plasticity may also apply to presynaptic forms of plasticity. Like postsynaptic plasticity, presynaptic plasticity can be bidirectional (LTP/LTD), and display input-specificity and associativity (Fig. 1). As with the postsynapse, metaplastic changes at the presynaptic compartment can alter the threshold of presynaptic plasticity and/or homeostatic plasticity can adjust the strength of the network in response to perturbations (for a recent review, see [5]). Lastly, presynaptic plasticity may also involve structural changes and may require presynaptic protein synthesis.

Bidirectionality

Postsynaptic LTP/LTD typically relies on bidirectional modulation of protein kinases likely triggered by high vs. low calcium rise in the postsynaptic compartment [6]. Similarly, strong

or weak repetitive activity at the MF-CA3 synapse, presumably by elevating presynaptic calcium levels in a fast or slow manner, increases or decreases cAMP/PKA activity, thereby inducing presynaptic LTP/LTD, respectively [7]. Bidirectional cAMP/PKA modulation via presynaptic dopamine-1 receptors (D₁R) and type 2/3 metabotropic glutamate receptors (mGluR2/3) determines the sign of plasticity at glutamatergic terminals in the basolateral amygdala (BLA) [8]. At MF-CA3 interneuron synapses, presynaptic mGluR7 can act as a metaplastic switch to control the sign of plasticity by regulating cAMP sensitivity [9, 10]. While endocannabinoids (eCBs) typically mediate presynaptic LTD (eCB-LTD) [11], recent evidence suggests eCBs support bidirectionality (eCB-LTP) at cortico-striatal synapses [12, 13]. While some synapses express either presynaptic LTP or LTD, bidirectional presynaptic plasticity may be an important way to increase the dynamic range of synaptic transmission in response to experience. It remains unclear how most forms of plasticity are reversed or switched off.

Presynaptic associativity and coincidence detection

A key feature of postsynaptic, NMDAR-dependent Hebbian plasticity is associativity wherein NMDARs act as coincidence detectors of both postsynaptic depolarization and presynaptic glutamate release. However, associativity is not an exclusive property of postsynaptic LTP/LTD. The presynaptic terminal can integrate signals (e.g. retrograde messengers) with presynaptic activity [2], thereby ensuring input-specificity –i.e. only active terminals receiving the signal undergo plasticity– when the signal is a diffusible molecule. This mechanism has been proposed for eCB-LTD in visual cortex [14] dorsal striatum [15], and hippocampus [16]. In classical postsynaptic LTP/LTD, calcium elevations act as a trigger of plasticity by activating a number of signaling cascades in the postsynaptic compartment. Presynaptic calcium elevations, via VGCCs or presynaptic NMDARs (preNMDARs), activate metabolic cascades that facilitate the induction of eCB-LTD.

Unlike postsynaptic NMDAR-dependent plasticity, preNMDARs may play a permissive or modulatory role. Likely acting as coincidence detectors, preNMDARs contribute to presynaptic spike-timing dependent (STDP) forms of LTD (a.k.a. tLTD) wherein action potentials in close precession of excitatory postsynaptic potentials result in eCB-LTD particularly at synapses in juvenile animals [14, 17–19]. In *Xenopus* optic tectum, activation of preNMDARs by glutamate release from nearby excitatory synapses triggers presumably eCB-independent LTD of GABA release [20]. Intriguingly, preNMDAR-mediated tLTD at visual cortex layer 4-2/3 synapses is suppressed by visual experience, and sensory deprivation in adulthood, by increasing preNMDAR expression and glutamate release, reinstates tLTD [19]. Thus, the precise mechanism of preNMDAR action in long-term plasticity is synapse-specific and may depend on the developmental state or history of the synapse. More research is needed to assess the contribution of preNMDARs to presynaptic Ca²⁺ and determine whether preNMDARs play a metabotropic or ionotropic role in long-term plasticity. Astrocytes may also play a role in coincidence detection and presynaptic plasticity, via mechanisms involving gliotransmitters and eCB release [17, 21–23].

Structural Changes

Like postsynaptic dendritic spines, axons and presynaptic terminals also undergo long-term experience and activity-dependent structural plasticity in the adult mammalian brain [24–26]. These structural changes could underlie functional alterations of presynaptic strength, for example, via changes in the size or number of active zones, the number of vesicles recruited or docked, or through changes in the distance between synaptic vesicles and presynaptic VGCCs [27–31]. Aberrant presynaptic structural plasticity may also contribute to disease pathology such as in epilepsy or drug addiction [32, 33].

Structural plasticity of the presynaptic and postsynaptic elements is likely coordinated, as indicated by the correlated enlargement of presynaptic boutons, postsynaptic spines, and postsynaptic current [34, 35]. Following NMDAR-dependent LTP in hippocampal area CA1 *in vitro*, the number of axonal boutons with a single postsynaptic structure decreased by nearly a third, while the number of non-synaptic and multi-synaptic boutons remained unchanged [36]. It remains unknown how LTP of the postsynapse is conveyed to the presynaptic terminal to elicit structural changes [36]. Retrograde messengers like nitric oxide, arachidonic acid, and eCBs may act as one potential mechanism of pre-post coordination of structural plasticity [37, 38].

Presynaptic structural plasticity is cell-type and synapse-specific [39]. In the amygdala, fear conditioning results in increased variability in size of neighboring boutons, in contrast to the coherent bouton size in naïve conditions [40]. Retention of critical sensory information may require relative stability of boutons. For example, in the barrel cortex 80% of boutons persist for 12 months even in enriched sensory environments [41]. More studies are required to determine the precise functional relevance of structural plasticity and carefully distinguish causal versus homeostatic structural changes.

Local presynaptic protein synthesis

Postsynaptic local protein synthesis is believed to be critical in cementing long-term changes in synaptic strength and has been postulated to underlie input-specificity in plasticity [42]. Functionally, presynaptic local protein synthesis could be important for rapid, synapse-specific, long-term response to cues, for example through enduring modification of the presynaptic compartment. While some forms of presynaptic plasticity are suggested to rely on protein synthesis [43–46], the long-standing dogma is that adult axons do not contain ribosomes and therefore cannot synthesize protein. However, recent decades have turned up an abundance of evidence to the contrary [47].

A functional role for local presynaptic protein synthesis has been recently demonstrated in inhibitory eCB-LTD, and ribosomes were identified in inhibitory interneuron terminals using super-resolution microscopy in the mature rodent hippocampus [48]. New work using the Ribotag transgenic mouse identified immunogold labeling of ribosomes in the presynaptic compartment of adult retinal ganglion cells [49]. Additionally, RNA-binding proteins are localized to adult presynaptic terminals, but their role in the regulation of presynaptic protein synthesis in response to activity and experience remains poorly understood [50]. Presumably

the presynaptic terminal contains relatively few mRNA species whose translation could act as a molecular switch in pathways involved in plasticity of neurotransmitter release. Future research should examine the identity of locally synthesized transcripts in presynaptic plasticity. Moreover, the spatial and temporal dynamics of protein synthesis in axons also deserves a thorough characterization, e.g. whether presynaptic ribosomes associate with endoplasmic reticulum. New imaging technologies that allow unprecedented spatial and temporal resolution of protein synthesis make it an opportune time to begin to address these questions [51–53].

Presynaptic plasticity in circuit function and behavior

Assessing the precise contribution of presynaptic LTP/LTD in a particular circuit function or behavior requires selective manipulation of plasticity, a feat hard to achieve without affecting basal synaptic transmission or other processes. New tools such as retrograde viral tracers, optogenetics, and pharmacogenetics have enabled the study of presynaptic plasticity within short and long-range circuits. Because of limited space, here we will focus on a few recent examples in the hippocampus and amygdala where long-term presynaptic plasticity shapes circuit function and behavior.

Disinhibition can robustly shift the excitatory-inhibitory balance in a network, and frequently involves presynaptic plasticity [54]. In the entorhinal cortex-hippocampus circuit, input-timing dependent plasticity (ITDP), a form of heterosynaptic plasticity at Schaffer collateral (SC) to CA1 pyramidal cell synapse (SC-CA1) that is induced by pairing SC and entorhinal cortex (EC) inputs, involves both LTD of GABA release from cholecystokinin (CCK)-positive interneuron and SC-CA1 LTP [55]. ITDP requires precise timing of both SC inputs onto CCK interneurons and EC inputs to postsynaptic CA1 pyramidal cells. This timing (20 ms) coincides with the inherent delay in the cortico-hippocampal circuit and the γ -oscillation period. Presynaptic eCB-iLTD of feedforward inhibition (FFI) in CCK interneurons may enable activation of CA1 pyramidal cells to facilitate information salience [55]. A long-range inhibitory projection from the EC further contributes to FFI, as silencing these inputs blocks the induction of ITDP and alters fear memory formation [56].

After weak fear conditioning, STDP induces LTD at lateral amygdala (LA) excitatory projections onto GABAergic intercalated cells (ITCs) [57]. Mechanistically, LTD results from presynaptic D₄R-mediated LTP of GABA release in dorsal ITC. Moreover, D₄R-LTD is impaired in a mouse model displaying post-traumatic stress disorder (PTSD)-like behavior and may be important for selective fear memory storage [57]. Parvalbumin (PV)-positive interneurons in the LA receive robust excitatory input and mediate powerful FFI onto principal neurons. After fear conditioning, both excitatory inputs –which carry cued auditory information– and inhibitory output of PV interneurons are persistently reduced in a presynaptic manner as indicated by a reduction in paired-pulse ratio [58]. The reduction of GABA release onto LA principal neurons may facilitate subsequent amygdala recruitment by sensory stimuli, thereby contributing to fear learning. Extinction learning is associated with reduced synaptic efficacy in projections from the medial prefrontal cortex to the basolateral amygdala, whereas inhibition remains intact. Presynaptic LTD likely underlies this reduction in excitatory drive [59].

Presynaptic plasticity in disease

Growing evidence suggests that presynaptic plasticity can be altered in brain disease. As with other forms of plasticity, it is unclear whether aberrant presynaptic plasticity contributes causally or is a consequence of the disease. Genome-wide analysis identified the microRNA-137 (MIR137) locus with schizophrenia, and MIR137 gain-of-function *in vivo* results in impaired induction of presynaptic MF-LTP and hippocampus-dependent learning and memory task acquisition [60]. In addition, changes in the CA2 region of the hippocampus may underlie cognitive and social deficits associated with schizophrenia. The 22q11.2 mouse model of schizophrenia, which recapitulates these changes in CA2, is associated with impaired presynaptic δ -opioid receptor-dependent LTD of GABA transmission and deficits in social learning [61]. Taken together, these studies suggest a potential link between presynaptic plasticity and schizophrenia. Autism spectrum disorders (ASDs) are associated with synaptic deficits, including imbalanced excitation/inhibition ratios and impaired synaptic plasticity [62]. While most research has focused on postsynaptic deficits, disrupted presynaptic plasticity may be another consequence of ASDs. In the *Fmr1* knockout mouse model of Fragile X syndrome, the most frequent monogenic cause of ASD, presynaptic eCB-LTD is reportedly increased at hippocampal inhibitory synapses [63], but impaired at excitatory synapses in NAc and PFC [64]. The reason for this discrepancy is unclear, although dysregulation in group I mGluR-dependent production of eCB seems to underlie these phenotypes. *Fmr1* knockout mice also show impaired presynaptic LTP of excitatory transmission in the anterior cingulate cortex [65]. Lastly, altered presynaptic plasticity has been reported in animal models of neurodegenerative diseases, including Alzheimer's disease [66, 67] and Parkinson's disease [68]. Whether and how presynaptic plasticity alterations contribute to neurodegenerative diseases in humans remains to be determined.

Exposure to drugs of abuse can hijack presynaptic plasticity in brain areas critically involved in drug-adaptive behaviors [69, 70]. A single *in vivo* exposure to drugs of abuse in mice disrupts presynaptic LTD for a few days; e.g. eCB-LTD in the hippocampus and nucleus accumbens (NAc) following Δ^9 -THC [116], and MOR- and eCB-mediated LTD following the opioid painkiller, oxycodone [71]. Adolescent mice exposed daily to a CB₁R agonist show impaired presynaptic eCB-LTD and mGluR2/3-mediated LTD in the prefrontal cortex (PFC) lasting into adulthood [72]. Repeated exposure to cocaine in rodents disinhibits dopamine neurons of the ventral tegmental area (VTA) in two ways: by facilitating the induction of presynaptic eCB-LTD of inhibitory inputs to dopamine VTA neurons [73] and indirectly by promoting LTP of GABA release from medium spiny neurons of the NAc projecting onto local interneurons that inhibit VTA dopamine neurons [74]. In addition, exposure to morphine, by activating presynaptic MORs, prevents nitric oxide-dependent LTP of GABA release onto VTA dopamine neurons [75]. A recent study reported that chronic cocaine exposure induces presynaptic plasticity of excitatory PFC inputs into the NAc [76]. Stressors can also alter drug-seeking behavior via presynaptic GABAergic plasticity and administration of κ -opioid receptor antagonists can diminish these effects [77].

Conclusions

Presynaptic plasticity is mechanistically diverse and widely expressed throughout the brain. By modifying excitatory and inhibitory transmission, presynaptic plasticity can robustly reshape circuit function and participate in several brain functions such as cognition, motivation and emotion. Despite decades of research, the precise molecular basis underlying long-lasting increases or decreases of neurotransmitter remains largely elusive. Key properties previously described for postsynaptic long-term plasticity are also observed at presynaptic forms of plasticity. While some synapses preferentially express pre or postsynaptic plasticity, these two forms can coexist at the same synapse. It remains unclear why evolution has selected for pre or postsynaptic plasticity, and why some synapses, and the circuits they are embedded in, prefer one mechanism over another. Having two mechanistically different forms of plasticity likely provides additional flexibility in encoding information. New developments in super-resolution microscopy that allow us to clearly distinguish pre- from postsynaptic compartments [78] and methods to genetically dissect inputs from distant brain regions [79] will likely drive advances in understanding presynaptic plasticity. Lastly, deficits in presynaptic plasticity are emerging as potential causal targets of disease. Future research directed at understanding presynaptic plasticity mechanisms will likely drive discovery of new therapeutic interventions for diseases like addiction, ASDs and schizophrenia.

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Highlights

- Long-term presynaptic plasticity is vital for experience-dependent circuit function
- Presynaptic forms of plasticity share properties of classical postsynaptic plasticity
- The molecular basis of long-term changes in neurotransmitter release is still unknown
- Long-term presynaptic plasticity is impaired in brain diseases

Figure 1. Principles of long-term presynaptic plasticity

a. The sign of some forms of presynaptic plasticity can be mediated by high v. low calcium concentrations, eCB concentrations, and/or opposing kinase/phosphatase signaling pathways.

b. Coincidence detection in the presynaptic compartment is critical for some forms of presynaptic plasticity, via preNMDARs, postsynaptic retrograde messenger release and presynaptic receptor activation, and/or coincident activation of parallel signaling pathways. The calcium-dependent phosphatase, calcineurin, has been identified as a key mediator of

presynaptic LTD, likely by promoting dephosphorylation of a presynaptic target (T) [16, 17, 22].

c. Presynaptic plasticity may involve structural changes, including actin polymerization, insertion or removal of release sites and/or changes in vesicle distribution.

d. Local presynaptic protein synthesis is one mechanism for achieving rapid, synapse-specific response to local signaling cues. The identity of newly synthesized proteins and how they regulate neurotransmitter release in a long-term manner remain unknown.