

 Cell biology in neuroscience

The interplay between Hebbian and homeostatic synaptic plasticity

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Synaptic plasticity, a change in the efficacy of synaptic signaling, is a key property of synaptic communication that is vital to many brain functions. Hebbian forms of long-lasting synaptic plasticity—long-term potentiation (LTP) and long-term depression (LTD)—have been well studied and are considered to be the cellular basis for particular types of memory. Recently, homeostatic synaptic plasticity, a compensatory form of synaptic strength change, has attracted attention as a cellular mechanism that counteracts changes brought about by LTP and LTD to help stabilize neuronal network activity. New findings on the cellular mechanisms and molecular players of the two forms of plasticity are uncovering the interplay between them in individual neurons.

Introduction

Synapses are highly specialized cell–cell junctions that mediate communication between neurons in the brain. As such, signal transmission across synapses is integral to a variety of cognitive processes from attention, perception, learning, and memory to decision making. A key feature of synaptic transmission underlying such cognitive functions is its plasticity: depending on the pattern of synaptic activation and the overall level of neural network excitation, the efficacy of synaptic transmission (called “synaptic strength”) is dynamically changed, which transforms information processing in neural circuits. Over the past decades, huge advances have been made toward understanding the fundamental basis of synaptic transmission. Synaptic transmission is initiated at the presynaptic terminal, where the arrival of an action potential triggers Ca^{2+} influx to set off synaptic vesicle

exocytosis at the active zone located opposite to the postsynaptic terminal. The exocytically released neurotransmitters travel across the narrow synaptic cleft and bind to the neurotransmitter receptors enriched at the surface of the postsynapse; this changes the membrane potential to either propagate the electrical signal (excitatory synaptic transmission, mostly mediated by glutamate in the central nervous system) or to block it (inhibitory synaptic transmission, mostly mediated by GABA in the central nervous system). The majority of glutamatergic excitatory synapses in the brain are formed on small, distinct structures called “spines” that protrude from the dendrite. Glutamate receptors are found concentrated at the head of the spine facing the presynaptic terminal, within a specialized protein scaffold termed the postsynaptic density (PSD).

Synaptic efficacy has two key determinants: the likelihood that synaptic vesicles undergo exocytosis in response to an action potential—the neurotransmitter release probability, p_r —and the number of functional postsynaptic receptors available to bind to the released transmitters (Del Castillo and Katz, 1954; Lisman et al., 2007). Changes to these two parameters over various time scales give rise to different forms of synaptic plasticity (Abbott and Regehr, 2004; Lisman et al., 2007). Interestingly, the size of a synapse in general seems to correlate with synaptic efficacy. For example, at glutamatergic synapses, the stronger the synapse, the larger the spine head and the PSD, where more glutamate receptors are present (Matsuzaki et al., 2004). On the presynaptic side, the larger PSD is matched by a larger active zone with a higher p_r , where more release-ready synaptic vesicles are docked (Schikorski and Stevens, 1997; Murthy et al., 2001). It is thus not surprising that changes in synaptic strength, of p_r , and the number of glutamate receptors often accompany morphological plasticity; notably, the changes in spine shape are highly conspicuous and readily imaged using fluorescent reporters (Yuste and Bonhoeffer, 2001; Alvarez and Sabatini, 2007; Cingolani and Goda, 2008).

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Abbreviations used in this paper: AMPAR, AMPA-type glutamate receptor; CaMKII, Ca^{2+} /calmodulin-dependent protein kinase II; LTD, long-term depression; LTP, long-term potentiation; NLG, neuroligin; NMDAR, NMDA-type glutamate receptor; NMJ, neuromuscular junction; PSD, postsynaptic density.

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Durable forms of synaptic plasticity known as Hebbian plasticity, including long-term potentiation (LTP) and long-term depression (LTD), have been extensively studied as cellular correlates of some types of memory (Bliss and Collingridge, 1993; Bi and Poo, 2001; Sjöström et al., 2008; Collingridge et al., 2010; Cooper and Bear, 2012). Induction of Hebbian plasticity is associative in requiring correlated firing of the presynaptic and the postsynaptic neurons, and the change in synaptic strength is rapid, specific to active inputs, and can last for hours to months (Bliss and Lomo, 1973; Andersen et al., 1977; Lee et al., 2009). Moreover, Hebbian plasticity can provoke positive feedback processes. That is, once LTP is induced, potentiated synapses can be excited to undergo further potentiation with greater ease than before the LTP induction, and reach an unstable state prone to hyperexcitation (Turrigiano and Nelson, 2000; Cooper and Bear, 2012). Similarly, upon inducing LTD, unchecked synaptic depression could lead to pathological synapse elimination (Collingridge et al., 2010; Cooper and Bear, 2012). In contrast to LTP and LTD, which are potentially prone to instability, homeostatic synaptic plasticity operates as a compensatory, negative feedback mechanism to maintain network stability (Turrigiano and Nelson, 2000; Turrigiano, 2008; Pozo and Goda, 2010). Homeostatic plasticity is not only important under conditions of elevated excitability when it reduces synaptic strength to help prevent runaway excitation, it can also increase synaptic strength under conditions of chronic activity suppression to increase synaptic gain and prevent unnecessary synapse silencing and loss.

Although the need for homeostatic processes have been framed in association with Hebbian changes (Turrigiano and Nelson, 2000), most studies to date have examined the mechanisms of homeostatic synaptic plasticity separately from that of Hebbian plasticity (Turrigiano, 2008; Pozo and Goda, 2010). Our knowledge of homeostatic synaptic plasticity mechanisms has significantly expanded in recent years, and the field may be ready for considering when, where, and how neurons express the two functionally opposing forms synaptic plasticity. We begin our review by highlighting some recent studies that provide insights into the possible interplay of Hebbian and homeostatic plasticity.

Balancing Hebbian and homeostatic synaptic plasticities

In Hebbian plasticity, synaptic strength change is confined to active synapses, a property that is referred to as “input specificity”; this feature presumably represents event-specific changes that are requisite for the storage of discrete information (Bliss and Lomo, 1973; Andersen et al., 1977; Bi and Poo, 2001; Sjöström et al., 2008). Conversely, homeostatic synaptic plasticity has been generally considered to be a slow process and expressed globally such that all synaptic inputs received by a given neuron are scaled equally. In this way, homeostatic synaptic plasticity can preserve the relative differences in synaptic strengths resulting from input-specific Hebbian changes. However, increasing evidence supports the idea that homeostatic synaptic strength changes can be also rapid and local, and both global and local homeostatic mechanisms might operate in parallel in a nested manner (Turrigiano, 2008; Pozo and Goda, 2010). The presence of fast and local

forms of homeostatic synaptic plasticity, in turn, raises questions about how the compensatory mechanisms could be implemented without interfering and in concert with Hebbian changes. This is paradoxical given that both processes target the same synaptic strength parameters (p_r and the number of functional postsynaptic receptors) to elicit plasticity, yet in opposite directions.

In one possible scenario that has been suggested previously, Hebbian plasticity at a single synapse could be counterbalanced by synaptic strength changes in the neighboring synapses of the opposite polarity (Rabinowitch and Segev, 2008). For example, a synapse expressing LTP could be adjoined by synapses whose strengths are weakened by homeostatic mechanisms; such changes could be visible as an enlarged spine with a larger PSD carrying more glutamate receptors that are surrounded by thinner spines, which have lost some of their glutamate receptors (Fig. 1). A recent study in the rat cerebellum provides evidence that this could be the case. Lee et al. (2013a) examined, following motor skill training, the formation of specialized parallel fiber presynaptic terminals that contain at least two active zones, called multiple-synapse boutons, which contact two distinct spines in dendrites of Purkinje cells. Importantly, motor learning promotes the incidence of multiple-synapse boutons on pairs of spines originating from the same dendrite rather than from different dendritic segments, such that the potency of synapses in eliciting dendritic excitation is locally enhanced. Furthermore, in the trained animal group, PSD area of spines adjacent to multiple-synapse boutons are significantly smaller, which is suggestive of coordinated weakening of adjacent inputs (Lee et al., 2013a). Therefore, upon motor learning, local compensatory change at the neighboring synapses could effectively balance local dendritic activity by redistributing the weight of select inputs to help maintain excitability while allowing for local synaptic strengthening. The functional validation of such structurally inferred local coordination of synaptic strengthening and weakening awaits further studies. A similar coordination of balanced changes in synapse size and number has been also reported for LTP in hippocampal CA1 dendrites (Bourne and Harris, 2011).

The local compensatory change in synaptic strength associated with LTP is reminiscent of heterosynaptic LTD reported in the hippocampus, which is a depression of synaptic strength at inactive inputs that accompanies LTP at the stimulated input (Lynch et al., 1977; Schuman and Madison, 1994; Scanziani et al., 1996). Implicit with the occurrence of heterosynaptic changes at inactive inputs is the idea that LTP is not necessarily input specific. If heterosynaptic LTD could be interpreted as a homeostatic, compensatory change in response to LTP of stimulated inputs, albeit being expressed with similar kinetics as LTP, then the distinction between Hebbian and homeostatic forms of synaptic plasticity becomes blurred. Delineating the molecular mechanisms involved for each type of synaptic strength change would help in distinguishing specific forms of synaptic plasticity.

Local, input-specific homeostatic synaptic plasticity

Another unique manner of expression of local homeostatic synaptic plasticity has been described in the hippocampal circuit. A recent study in dissociated hippocampal culture has identified a surprising developmental shift in homeostatic synaptic plasticity

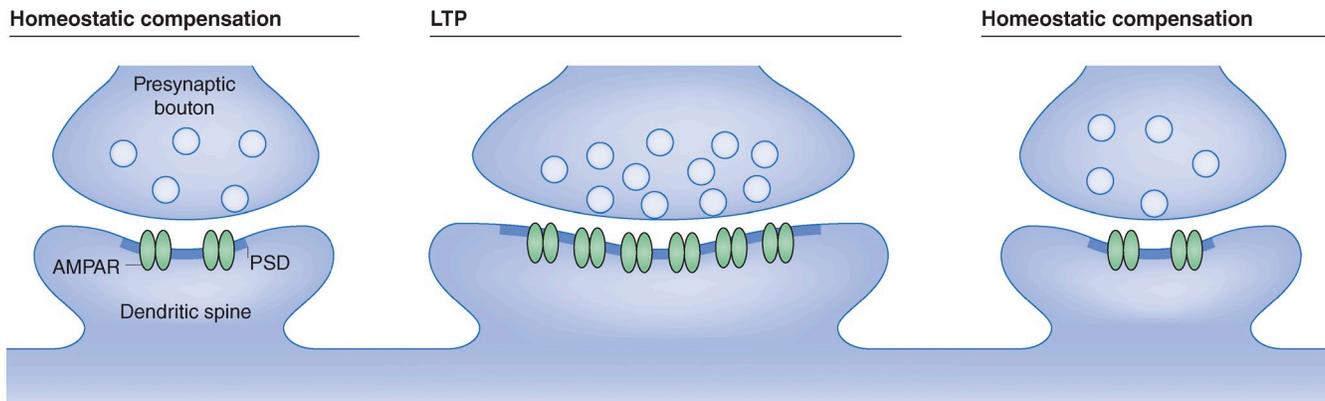


Figure 1. **Compensation of Hebbian plasticity at neighboring synapses.** A synapse undergoing LTP (middle) is adjoined by weaker synapses (left and right). Compensatory depression of synaptic strength of synapses adjacent to a potentiated synapse could be a form of homeostatic compensation to help maintain local dendritic activity (see text).

from a global to a locally expressed form (Lee et al., 2013b). Specifically, in relatively young cultures of the sort used for many homeostatic synaptic plasticity studies to date (~11 d *in vitro*), chronic modulation of network activity elicits global bi-directional changes in synaptic strengths in all excitatory neuron types present. However, in mature cultures that have been kept *in vitro* for at least 3 wk, the expression of homeostatic synaptic plasticity becomes apparently restricted to CA3 hippocampal neurons, and moreover, only to synapses proximal to the cell bodies of CA3 neurons. These synapses display features of giant mossy fiber synapses containing multiple release sites that form between dentate granule cells and CA3 neurons in the hippocampus, which are particularly effective in driving CA3 neuron excitation and its output neurons (Lawrence and McBain, 2003). Therefore, homeostatic plasticity at these highly potent giant CA3 mossy fiber synapses could be sufficient to provide the necessary compensatory adjustments for the Hebbian synaptic strength changes at other small synapses of the hippocampal circuit.

Limiting the expression of homeostatic synaptic plasticity to the most potent connection in driving the circuit could be an efficient way for simplifying the molecular mechanisms of homeostatic regulation, as only one synapse type needs to harness the cellular response to changes in network activity. Nevertheless, mossy fiber synapses are also capable of expressing LTP (Bortolotto et al., 2005), and how signals for adaptive homeostatic plasticity are discriminated from those required for LTP remains to be examined. Furthermore, chronic activity manipulation of mature hippocampal circuits in different experimental preparations, such as *in vivo* (Echegoyen et al., 2007) and slice cultures (Mitra et al., 2012), have reported of alterations in synaptic strengths of connections other than those of mossy fiber to CA3 synapses. The apparent restriction of the expression of homeostatic plasticity to mossy fiber boutons of CA3 neurons in cultured neurons warrants a closer look in preparations that better preserve the native synaptic connectivity.

Influence of homeostatic synaptic plasticity on subsequent LTP

A recent work in the hippocampus has addressed the interaction between homeostatic synaptic plasticity and LTP over different

time domains (Arendt et al., 2013). At excitatory synapses between CA3 and CA1 neurons, chronic suppression of network activity with tetrodotoxin (TTX; a blocker of sodium channels and hence of action potentials) increases postsynaptic strength by recruiting additional AMPA-type glutamate receptors (AMPA-type glutamate receptors) that mediate the majority of basal glutamatergic synaptic transmission. One might expect that such an increase in synaptic strength could potentially occlude subsequent LTP. Surprisingly, however, the authors find that LTP is enhanced if homeostatic synaptic plasticity is elicited first. The larger LTP is due at least in part to an increase by the TTX treatment in the number of synapses that are devoid of AMPARs but contain NMDA-type glutamate receptors (NMDARs). Such NMDAR-only synapses do not respond to basal release of glutamate and are silent under basal conditions; LTP induction unsilences these synapses by inserting AMPARs. Therefore, the homeostatic increase in the number of silent synapses serves to increase the overall magnitude of subsequently induced LTP. Whether AMPAR insertion during LTP is biased toward silent synapses or those with less AMPAR content, and if so, how, are not clear.

TTX-induced synaptic scaling of AMPARs is thought to be global in affecting all synapses proportionately. In contrast, it is not known if the formation of NMDAR-only silent synapses is also global in their distribution across the entire dendritic tree. To enable LTP that is input specific yet unsilences NMDAR-only synapses, it would be of interest to determine how silent synapses are formed in the first place so that active inputs can have access to them when undergoing LTP. In addition, although this study has examined the consequence of homeostatic plasticity on subsequently triggered LTP, it remains to be determined how the two forms of plasticity might compete with each other at individual synapses if they are triggered more closely in time. Furthermore, given that slice cultures used by Arendt et al. (2013) are fairly young (5–7 d *in vitro*), it would be of interest to test whether the propensity for inducing silent synapses by chronic activity silencing is a developmental feature and if the rules are different for mature hippocampal circuits.

Thus far, we have discussed the possible interplay of Hebbian and homeostatic plasticity from a cellular viewpoint. Some

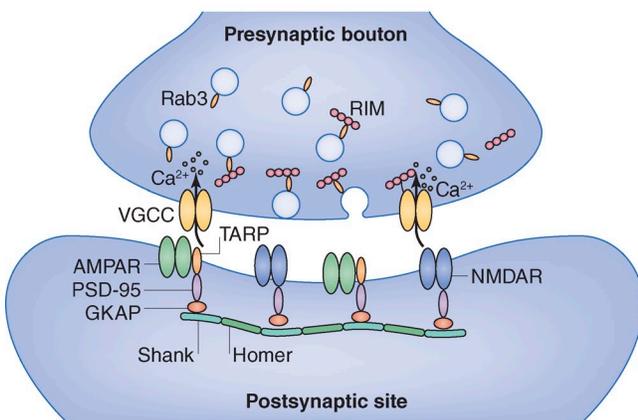
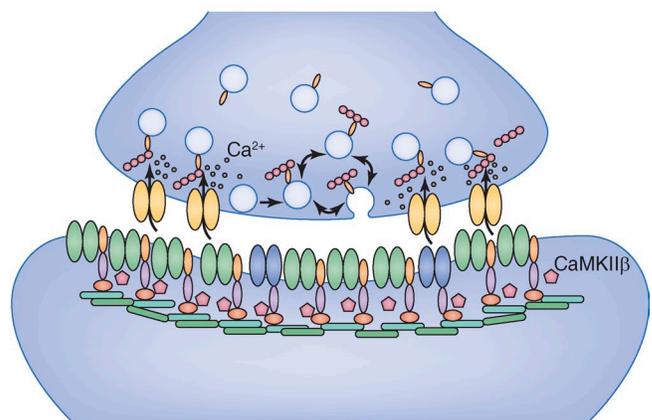
Basal activity**Chronic inactivity**

Figure 2. Homeostatic regulation of synaptic strength. (Left) RIM proteins are central organizers of the active zone. Under basal conditions, these proteins are essential for synaptic vesicle docking and priming and for the recruitment of Ca^{2+} channels to the active zone. RIM proteins interact with both Ca^{2+} channels (VGCC) and Rab3. (Right) Adaptation to inactivity is mediated by (a) an enhancement of presynaptic Ca^{2+} influx, probably due to a RIM-dependent increase in presynaptic voltage gated Ca^{2+} channel density at the active zone, and (b) by a RIM/Rab3-dependent regulation of synaptic vesicle docking/priming step that increases the readily releasable pool of synaptic vesicles and a Rab3-dependent control of the synaptic vesicle cycle. Postsynaptically, chronic activity blockage increases postsynaptic strength by recruiting additional AMPA-type glutamate receptors (AMPA). CaMKII β controls accumulation of the scaffolding molecule GKAP at synapses, which in turn regulates the synaptic levels of the scaffolding molecules PSD-95 and Shank to anchor AMPARs, thereby controlling homeostatic scaling.

of the characteristic features that have been thought to be unique to Hebbian or homeostatic synaptic plasticity are not necessarily so. Therefore, the distinction between these two classes of synaptic plasticity may not be as clear-cut as has been previously accepted. A better knowledge of molecular mechanisms can give us more precise tools for discriminating between the two processes and hence in better understanding their interaction. We now highlight some of the recent advances in identifying the molecular players and mechanisms involved in these durable forms of synaptic plasticity.

Molecular players of long-lasting changes in presynaptic strength

One of the most common paradigms used to elicit homeostatic synaptic plasticity is the chronic pharmacological treatment of neuronal cultures to block synaptic activity (Turrigiano, 2008). Adaptation to inactivity involves a compensatory enhancement of presynaptic strength, as suggested by the increase in the rate of spontaneous synaptic vesicle fusion, vesicle recycling, and p_r (Bacci et al., 2001; Murthy et al., 2001; Thiagarajan et al., 2005). How might changes in presynaptic strength occur? A recent study by Zhao et al. (2011) supports the importance of presynaptic Ca^{2+} influx in the homeostatic adaptation to inactivity. By using, in dissociated hippocampal cultures, a new optical approach that combines a Ca^{2+} reporter localized to synaptic vesicles (SyGCaMP2) and a pH-sensitive reporter of vesicle fusion (SypHy), the authors find that activity block causes a compensatory increase in action potential-evoked Ca^{2+} entry to the presynaptic terminal and the p_r (Zhao et al., 2011). The increase in Ca^{2+} influx could be at least in part mediated by an increase in the number of voltage-gated P/Q type Ca^{2+} channels (Lazarevic et al., 2011). Mounting evidence points to a central role for RIM proteins located at the active zone in sequestering Ca^{2+} channels at release sites via a PDZ domain interaction (Kaeser et al., 2012). Accordingly, in the

giant synapse of the auditory system called the Calyx of Held, conditional removal of all RIM1/2 isoforms reduces the presynaptic Ca^{2+} channel density (Han et al., 2011). Similarly, the expression of RIM mutants at the *Drosophila* neuromuscular junction (NMJ) affects the Ca^{2+} -dependent release by altering the accumulation of Ca^{2+} channels at release sites (Graf et al., 2012). Taken together, changes in presynaptic Ca^{2+} influx via modulation of RIM activity could be a key target for the homeostatic modulation of presynaptic strength.

Do changes in neurotransmitter release machinery also contribute to homeostatic presynaptic plasticity? Again, RIM and its interacting proteins, Rab GTPases, which are essential for basal and activity-dependent release (Schoch et al., 2002), seem to hold a key to this problem. At the *Drosophila* NMJ, Rab3-GTPase activating protein (GAP) and Rab3 have been suggested to facilitate homeostatic up-regulation of presynaptic strength at a late stage of synaptic vesicle exocytosis by relieving an inhibitory control over homeostatic changes (Müller et al., 2011). Additionally, in a more recent study at the fly NMJ, homeostatic enhancement of neurotransmitter release is shown to require RIM-dependent increase in the readily releasable synaptic vesicles but not the RIM-dependent control of Ca^{2+} influx, which is otherwise required for basal synaptic transmission (Müller et al., 2012). The precise relationship between Rab3 signaling and RIM in the homeostatic control of presynaptic release remains to be delineated. Altogether, despite some differences in the detailed mechanisms between model synapses, presynaptic adaptation to inactivity is likely to involve two phenomena: an enhancement of Ca^{2+} influx, probably mediated by an increase in the number of presynaptic voltage-gated Ca^{2+} channels, and Rab3 and RIM-dependent modulation of neurotransmitter release (Fig. 2).

The role of Rab3 and RIM in regulating presynaptic strength is not only limited to homeostatic synaptic plasticity,

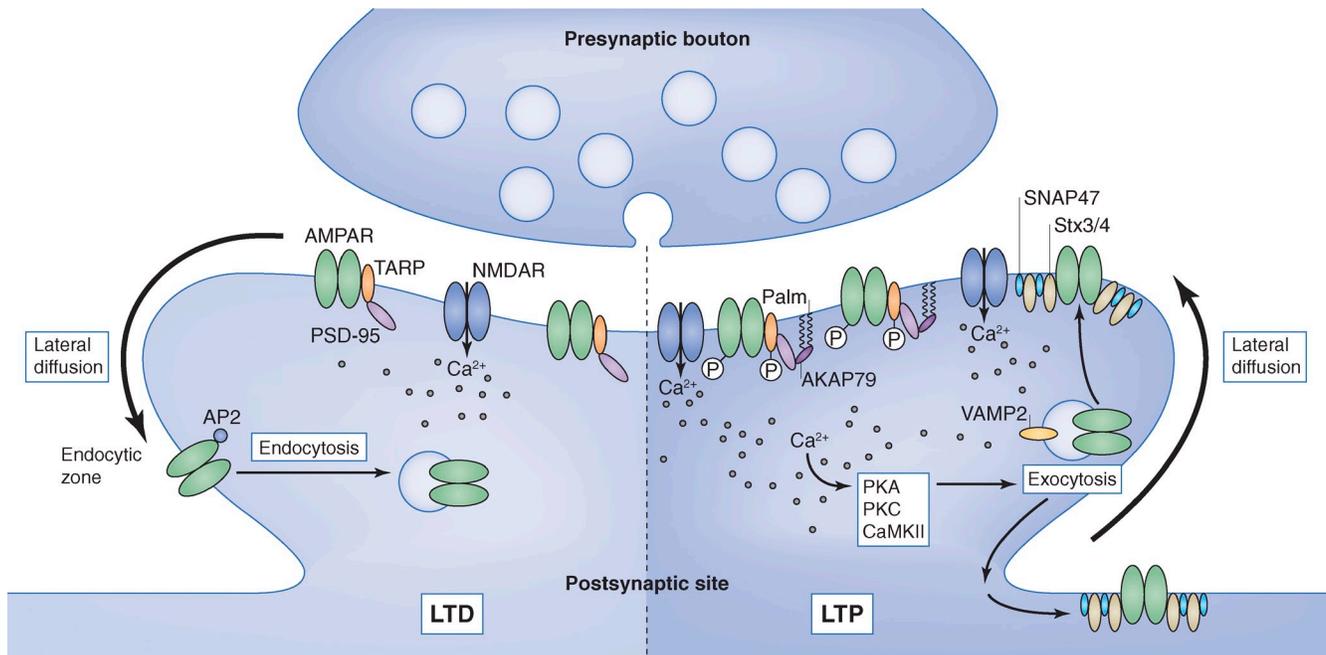


Figure 3. Molecular players and mechanisms involved in AMPAR trafficking during Hebbian plasticity. AMPAR lateral diffusion allows for a rapid increase in postsynaptic efficacy. (Right) For long-term potentiation (LTP) to occur, activation of NMDAR promotes Ca^{2+} influx, which is followed by activation of kinases (PKC, PKA, and CaMKII), phosphorylation of GluA1-containing AMPARs, and triggering of their exocytosis from intracellular pools. Palmitoylation (Palm) of AKAP79/150 promotes AMPAR trafficking and surface delivery. The specific location where AMPARs are incorporated at the surface is under debate; this could occur extrasynaptically or in spine heads. AMPAR exocytosis is mediated by members of the SNARE complex that differ from the ones that regulate presynaptic release. (Left) Long-term depression (LTD) is induced by a moderate level of Ca^{2+} influx and is characterized by the endocytosis of AMPAR from synapses. AMPAR are linked to clathrin via AP2. AKAP79/150 is depalmitoylated and removed from dendritic spines.

but it also extends to Hebbian plasticity. RIM1 α and two Rab3 isoforms, Rab3A and Rab3B, are essential for presynaptically expressed forms of LTP and LTD at both excitatory and inhibitory synapses (Castillo et al., 1997, 2002; Huang et al., 2005; Fourcaudot et al., 2008; Tsetsenis et al., 2011). Furthermore, the physiological relevance of these proteins is highlighted by their involvement in learning and memory (Powell et al., 2004; Tsetsenis et al., 2011). Thus, Hebbian and homeostatic plasticity seem to share the molecular pathways for their presynaptic induction and/or expression, with both processes capitalizing on an existing mechanism to implement changes in presynaptic strength.

The convergence of the presynaptic mechanism for the two opposing forms of synaptic plasticity raises questions about whether such sharing of mechanisms could serve to constrain both from occurring simultaneously. In other words, the presynaptic terminals, at least those with single active zones, may only express either a Hebbian or a homeostatic change. Beyond single release sites, neighboring active zones or boutons that are contacting different postsynaptic terminals could cooperate or compete in adjusting their release probability in response to Hebbian or homeostatic signaling.

Molecular players of long-lasting changes in postsynaptic strength

One of the main target mechanisms for regulating postsynaptic strength is the trafficking of AMPARs in and out of synapses (Fig. 3). Postsynaptic efficacy can be altered rapidly by lateral diffusion of receptors along the plasma membrane (Ehlers et al.,

2007; Heine et al., 2008; Patterson et al., 2010) and the exo-endocytic traffic of receptors between intracellular pools and the cell surface (Park et al., 2004, 2006; Yang et al., 2008; Patterson et al., 2010). Enhanced receptor exocytosis occurs during synaptic potentiation, whereas an increased rate of endocytosis is detected during synaptic depression. AMPARs incorporated to synapses during LTP contain the GluA1 subunit, and it has been reported that the two synaptic delivery routes are sequentially engaged: during ongoing LTP, most of the GluA1-containing AMPARs are incorporated to the PSD by lateral diffusion from extrasynaptic sites, but after potentiation, exocytosis of AMPARs from intracellular pools occurs (Makino and Malinow, 2009). Thus, highly mobile extrasynaptic AMPARs (Borgdorff and Choquet, 2002; Tardin et al., 2003) can serve as a readily available source for the synaptic recruitment of AMPAR during LTP, and replenishing these pools might be critical for LTP maintenance.

Stargazin and synaptic accumulation of AMPARs. AMPAR surface mobility and targeting to synapses are coordinated by protein interactions. For instance, Stargazin, a member of the transmembrane AMPAR regulatory protein (TARP) family, plays a pivotal role in this process. Stargazin directly interacts with both AMPARs and the scaffold protein PSD-95 via its PDZ-binding domain (Chen et al., 2000; Schnell et al., 2002). By using single-particle tracking in hippocampal neurons, Bats et al. (2007) have shown that AMPAR surface mobility and its synaptic stabilization is modulated by the Stargazin–PSD-95 interaction. Specifically, this interaction helps immobilize AMPARs at synapses and thus facilitate their

synaptic accumulation. Does Stargazin participate in activity-dependent AMPAR recruitment at synapses? High frequency stimulation has been shown to promote Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) dependent phosphorylation of Stargazin and its interaction with PSD-95, which in turn favors synaptic AMPAR accumulation (Opazo et al., 2010). In addition, Stargazin phosphorylation via CaMKII and PKC is crucial for the expression of LTP, whereas its dephosphorylation by PP1 plays a role in LTD (Tomita et al., 2005). Together, these data highlight a central function for Stargazin in the bidirectional regulation of postsynaptic strength in the hippocampus (Tomita et al., 2005).

The specific postsynaptic location where AMPARs are first inserted to the cell surface to mediate activity-dependent increase in postsynaptic strength has been debated. In hippocampal organotypic cultures and slices, the use of GluA1 tagged with a pH-sensitive probe, SEP-GluA1, as an optical reporter for activity-dependent AMPAR exocytosis, has revealed that this receptor subunit accumulates at synapses undergoing LTP via lateral diffusion (Yang et al., 2008; Makino and Malinow, 2009). In contrast, other studies show that SEP-GluA1 is exocytosed directly within dendritic spines upon synaptic stimulation (Kennedy et al., 2010; Patterson et al., 2010). A possible explanation for this discrepancy may be experimental differences in the imaging method and/or cultures and stimulation conditions.

Postsynaptic SNAREs and AMPAR exocytosis.

Which are the molecules involved in postsynaptic exocytosis of AMPARs? The SNARE proteins are essential for diverse forms of membrane fusion events in eukaryotic cells, and their role in synaptic vesicle fusion has been scrutinized (Südhof and Rizo, 2011). It is only recently that the contribution of the SNARE proteins in postsynaptic fusion events has become clear. The SNAREs Syntaxin-3 (Stx-3), Syntaxin-4 (Stx-4), SNAP-23, SNAP-25, SNAP-47, and Synaptobrevin-2 (VAMP2) are present in dendrites and/or enriched in spines (Holt et al., 2006; Kennedy et al., 2010; Suh et al., 2010; Jurado et al., 2013). By using an optical reporter to visualize exocytosis in hippocampal cultures, Kennedy et al. (2010) have shown that synaptic activity triggers the surface delivery of AMPARs at discrete Stx-4-enriched microdomains located immediately adjacent to the PSD (Kennedy et al., 2010). Interestingly, disrupting endogenous Stx-4 activity by shRNA or a dominant-negative peptide prevents activity-dependent AMPAR exocytosis in spines and blocks LTP, suggesting that Stx-4 is a central component of the postsynaptic SNARE machinery mediating the activity-dependent increase in postsynaptic strength. However, this idea has been recently challenged by an elegant study that has systematically analyzed the role of Stx-1, -3, and -4 and SNAP23, 25, and 47 in the exocytosis of AMPARs during LTP (Jurado et al., 2013). Using specific shRNAs to knock down the expression of each of these proteins in dissociated hippocampal cultures and acute slices, the authors show that Stx-3 knockdown, but not Stx-1 or Stx-4 knockdown, inhibits LTP, and also SNAP25 and SNAP47 knockdown but not SNAP23 knockdown, impair LTP. While during LTP, Stx-3, and SNAP-47 appear critical for the GluA1 delivery to the postsynaptic surface, SNAP-25 is required for the regulation of surface NMDAR

levels (Fig. 3). The differences in the role for Stx-4 identified in these two studies remain to be resolved.

The vesicular SNARE protein Synaptobrevin-2 is also postsynaptically expressed and is essential for regulating the abundance of synaptic AMPARs during LTP (Lledo et al., 1998; Jurado et al., 2013). Complexin, a protein that interacts with SNARE complexes and regulates Ca²⁺-dependent synaptic vesicle exocytosis at the presynaptic terminal, is required also for the regulated delivery of AMPARs during synaptic potentiation (Huang et al., 2000; Ahmad et al., 2012). In particular, the complexin binding sequence of Stx-3 is needed for LTP, highlighting a role of the Stx-3-complexin interaction in controlling AMPAR trafficking (Jurado et al., 2013). Interestingly, whereas presynaptic complexin acts as a cofactor for synaptotagmin-1 (Syt-1), postsynaptic complexin does not require Syt-1 for AMPAR delivery during LTP (Ahmad et al., 2012). Thus, other postsynaptically located synaptotagmin isoforms could take part in this signaling pathway, a possibility that remains to be explored. Altogether, the mechanism underlying AMPAR exocytosis is mediated by members of the SNARE complex that differ from the ones responsible for synaptic vesicle exocytosis, and the divergence likely contributes to their distinct properties, including the substantially different timing of these two exocytic events. Further studies are needed to clarify how the postsynaptic SNAREs and their interactors cooperate to fine-tune postsynaptic strength.

Post-translational modification of PSD proteins and regulating postsynaptic strength. The PSD contains a large number of scaffolding proteins including PSD-95, AKAP79/150, GKAP, and Shank. These proteins continually turn over by entering and leaving the PSD under basal conditions and in response to synaptic activity by mechanisms including protein phosphorylation, palmitoylation, ubiquitination, and proteasome-mediated protein degradation (Inoue and Okabe, 2003; Sheng and Kim, 2011). Changes in the PSD composition ultimately set postsynaptic strength by controlling AMPAR anchoring at the PSD. We now turn to discuss some recent advances that highlight the emerging role of post-translational modifications of PSD proteins in modulating synaptic strength and plasticity.

AKAP79/150 is a scaffold protein that interacts with both AMPAR and NMDAR via the membrane-associated guanylate kinase (MAGUK) scaffolds SAP97 and PSD-95; AKAP79/150 targets PKA, PKC, and calcineurin to regulate AMPAR phosphorylation and its traffic (Colledge et al., 2000; Tavalin et al., 2002; Lu et al., 2007; Tavalin, 2008; Bhattacharyya et al., 2009; Jurado et al., 2010; Sanderson and Dell'Acqua, 2011). Recently, it has been shown in hippocampal neurons that neuronal activity controls AKAP79/150 palmitoylation, which regulates its targeting to dendritic spines (and spine enlargement associated with LTP). Interestingly, preventing AKAP79/150 palmitoylation affects endosomal recycling, decreases GluA1 surface delivery, and impairs synaptic potentiation (Keith et al., 2012). Taken together, the scaffold interactions of AKAP79/150 (such as the link to PSD-95) and its dendritic spine targeting that is controlled by palmitoylation of AKAP are likely to play a role in bi-directional activity-dependent modulation of postsynaptic

AMPA receptors (Keith et al., 2012). It would be of interest to delineate the underlying mechanisms involved in this process.

The GKAP family of scaffolding proteins interacts with the guanylate kinase domain of PSD-95 and other scaffolding proteins including Shank to form a mesh of interacting proteins at the PSD. The abundance of GKAP and Shank proteins is regulated by synaptic activity: chronic activity elevation promotes the ubiquitination and proteasome-mediated degradation of GKAP and Shank scaffolds (Ehlers, 2003; Hung et al., 2010; Shin et al., 2012), whereas inactivity induces synaptic accumulation of GKAP in hippocampal neurons (Shin et al., 2012). Bi-directional changes in synaptic GKAP levels depend on the interplay of CaMKII isoforms: CaMKII α controls GKAP degradation during synaptic excitation, whereas the CaMKII β isoform promotes GKAP accumulation during synaptic inactivity (Fig. 2). In turn, GKAP turnover is critical for the activity-dependent regulation of synaptic levels of PSD-95 and Shank, and also for the bi-directional homeostatic synaptic scaling of AMPARs (Shin et al., 2012). Thus, GKAP plays an important part in orchestrating activity-dependent PSD remodeling and homeostatic plasticity.

Convergence of Hebbian and homeostatic mechanisms in controlling postsynaptic strength. Molecular mechanisms that mediate the changes in postsynaptic strength during Hebbian and homeostatic plasticity overlap for some molecules, whereas they remain distinct for others. For instance, LTP appears to involve synaptic incorporation of GluA1-containing AMPARs (Shi et al., 2001; Makino and Malinow, 2009; but see Granger et al., 2013). Similarly, the inactivity-dependent homeostatic increase of postsynaptic strength involves GluA1-containing AMPARs (Poza and Goda, 2010; Man, 2011), although in some cases, it requires the incorporation of GluA2-containing AMPARs to synapses (Gainey et al., 2009; Anggono et al., 2011). Notably, PSD-95 that regulates AMPAR traffic is differentially required for LTP and synaptic scaling. Knocking down PSD-95 prevents the compensatory scaling up of postsynaptic strength while having no effect on the induction and early expression of LTP (Ehrlich et al., 2007; Sun and Turrigiano, 2011). Similarly, TNF and β 3 integrin also show differential involvement in regulating synaptic AMPARs for the two forms of plasticity: they are required for homeostatic synaptic scaling but dispensable for LTP and LTD (Stellwagen and Malenka, 2006; Cingolani et al., 2008; McGeachie et al., 2012). Given that there may be multiple forms of homeostatic modulation of postsynaptic strength, and this coupled to distinct forms of Hebbian plasticity, the molecular repertoire of receptor modulation involved in postsynaptic plasticity may be highly complex.

Retrograde regulation of presynaptic strength

That the pre- and the postsynaptic strengths are coordinated in an activity-dependent manner (Tokuoka and Goda, 2008) suggest that changes on either side of the synapse are transmitted trans-synaptically. This idea is further supported by the sufficiency of chronic postsynaptic receptor blockade in modifying presynaptic function (Burrone et al., 2002; Thiagarajan et al., 2005). How might the postsynaptic cell modulate presynaptic

function? Dendrites can release a variety of messengers that act on presynaptic terminals to influence neurotransmitter release (Tyler et al., 2002; Jakawich et al., 2010; Lindskog et al., 2010; Ohno-Shosaku et al., 2012). Diffusible or secreted messengers, in principle, can cover a broad area over long time scales to coordinate changes in presynaptic function across many release sites, albeit some, such as nitric oxide, are short-lived. In contrast, synapse adhesion proteins, by directly bridging the pre- and the postsynaptic terminals, could mediate targeted modulation of presynaptic function resulting from postsynaptic activity at a particular synapse. Such a capacity for synapse-specific regulation may be crucial for coordinating the pre- and postsynaptic function of mature synapses across different connections with a shared output or input. Here, we highlight the trans-synaptic signaling mediated by two families of transmembrane adhesion molecules that regulate presynaptic strength: neuroligin–neurexin pairs and cadherins (Fig. 4).

Neuroligins (NLGs) are postsynaptically located synaptic adhesion molecules that have been recently established as important regulators of presynaptic strength. By interacting postsynaptically with PSD-95 and presynaptically with β -neurexin (Nrxn), NLG retrogradely regulates presynaptic neurotransmitter release (Futai et al., 2007). Importantly, an increase in synaptic activity drives the cleavage of postsynaptic NLG-1, causing a rapid destabilization of Nrxn1 β and reducing p_r in vivo (Peixoto et al., 2012; Suzuki et al., 2012). Protease-dependent modifications of synaptic adhesion molecules therefore provide an extra level of regulation of synaptic function. When, where, and how proteases are released or activated will be an important point to resolve in this respect.

A recent study in vivo underscores the importance of NLG-1 in regulating synapse number according to activity in a context-dependent manner (Kwon et al., 2012). Interestingly, in cortical layer 2/3 neurons, the density of functional synapses is determined not by the absolute level of NLG1 expression across all pyramidal neurons, but by the relative differences in its expression compared with neighboring neurons. This suggests of a competitive process in hand, and it is tempting to speculate that different levels of activity could dynamically alter the amount of NLG-1 either locally or in individual neurons. This then helps to increase p_r of presynaptic inputs to the neuron expressing higher NLG-1, which in turn further increases the excitation of the neuron and its synapse number. Consistent with such a role for NLG-1 in regulating synapse function involving a positive feedback process, NLG has been proposed to promote LTP and memory storage (Kim et al., 2008; Blundell et al., 2010; Shipman and Nicoll, 2012). A role of NLG in the homeostatic regulation of synaptic strength remains to be determined.

Cadherins are homophilically interacting cell adhesion molecules. They indirectly link to actin cytoskeleton via binding to β - and α -catenins and are involved in cell shape changes; they also engage in signaling pathways that are well characterized (Brigidi and Bamji, 2011). At synapses the N-cadherin– β -catenin complex is an important mediator of functional and morphological plasticity. For instance, disrupting N-cadherin adhesion blocks LTP and the plasticity-related spine enlargement

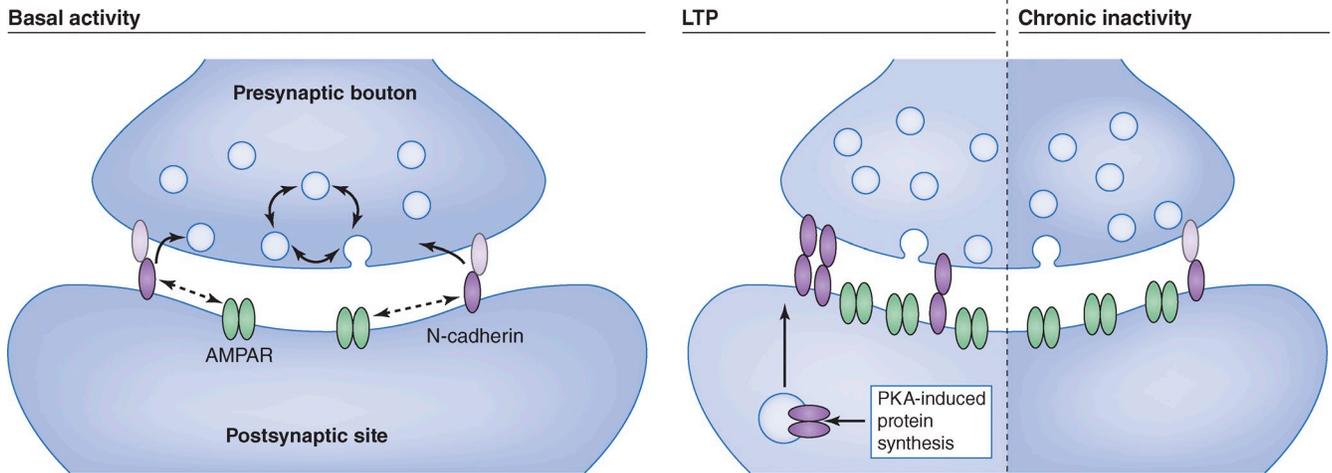


Figure 4. Basal and activity-dependent regulation of synaptic strength by N-cadherin. (Left) Under basal conditions, postsynaptic N-cadherin controls presynaptic strength by modulating synaptic vesicle recycling. Notably, the retrograde role of postsynaptic N-cadherin (purple) appears independent of the homophilic interaction with presynaptic N-cadherin (light purple). GluA2-containing AMPAR seems to be the postsynaptic effector; how these two molecules cooperate to regulate presynaptic strength is not clear (dashed arrows). A possible mechanism is the interaction of postsynaptic N-cadherin and/or GluA2 with a presynaptic partner, another postsynaptic adhesion protein, and/or the release of a soluble effector molecule to target synaptic vesicle recycling. (Right) Although N-cadherin homophilic adhesion is not required for the homeostatic up-regulation of p_r (right half), it plays a critical role in LTP (left half). During potentiation associated with LTP, N-cadherin proteins levels are enhanced as a consequence of PKA activity and protein synthesis.

(Bozdagi et al., 2000, 2010). Postsynaptic N-cadherin and β -catenin are also involved in homeostatic adaptation of synaptic strength in a cell-autonomous manner, and they contribute to the retrograde regulation of presynaptic function (Okuda et al., 2007; Vituriera et al., 2012).

A recent study using cultured hippocampal neurons has identified a differential requirement for postsynaptic N-cadherin and β -catenin in regulating presynaptic strength in trans: whereas N-cadherin is critical for regulating basal presynaptic strength, β -catenin has a role in adjusting presynaptic function upon chronic activity blockade. A requirement for central armadillo repeat region of β -catenin in homeostatic up-regulation of presynaptic efficacy suggests a potential contribution of gene transcription in this retrograde control of p_r (Vituriera et al., 2012). In contrast to postsynaptic β -catenin, interfering with postsynaptic N-cadherin has no effect on homeostatic up-regulation of p_r , but instead affects basal p_r accompanied by a significant reduction in synaptic vesicle endocytosis kinetics (Vituriera et al., 2012). Curiously, this trans-synaptic role of postsynaptic N-cadherin appears independent of the homophilic interaction with presynaptic N-cadherin or binding to postsynaptic β -catenin but requires GluA2-containing AMPARs (Fig. 4). Although N-cadherin and GluA2 can directly interact via their extracellular domains (Saglietti et al., 2007), how they cooperate to regulate presynaptic strength awaits to be clarified. Postsynaptic N-cadherin has also been reported to play a role in the NLG-1-dependent trans-synaptic regulation of presynaptic strength, albeit in immature neurons in vitro (Stan et al., 2010).

Altogether, the retrograde regulation of presynaptic function appears to involve cooperation between different synaptic adhesion systems, allowing for increased flexibility in fine-tuning of synaptic strength associated with or as required by expression of various forms of synaptic plasticity.

Matching of pre- and postsynaptic strengths upon expression of synaptic plasticity

Molecular mechanisms for retrograde control of presynaptic strength lend support to the idea that the pre- and the postsynaptic strengths match at individual synapses (Lisman et al., 2007). Indeed, recent studies in hippocampal cultures and rat neocortical slices have revealed the correlation of p_r and the abundance of postsynaptic receptors (Tokuoka and Goda, 2008; Hardingham et al., 2010; Kay et al., 2011; Loebel et al., 2013; also see Fisher-Lavie and Ziv, 2013). Nevertheless, in some cases, appreciable matching of the pre- and the postsynaptic strengths becomes evident only upon elevated activity (Tokuoka and Goda, 2008). This suggests that retrograde regulation of p_r , that operates under basal conditions, for instance by the postsynaptic N-cadherin described above, may not be sufficient by itself to match the pre- and the postsynaptic strengths of nascent synapses. Spontaneous activity, therefore, could drive activity-dependent retrograde modulation in concert with processes engaged under basal conditions to coordinate presynaptic and postsynaptic function.

Interestingly, the locus of expression of long-term synaptic plasticity is often biased toward one side of the synapse; for example, hippocampal CA1 LTP and LTD are acknowledged to involve primarily an increase or a decrease in the synaptic AMPAR content. This stipulates that durable forms of synaptic plasticity create a mismatch of pre- and postsynaptic function. A recent study in dissociated hippocampal culture has monitored the change in presynaptic vesicle turnover by surface biotinylation of synaptic vesicle components, while concurrently monitoring quantal amplitudes that reflect the number of AMPARs (Xu et al., 2013). Induction of mGluR-dependent LTD accompanies a decrease in quantal amplitude by facilitated endocytosis of AMPARs, and unexpectedly, presynaptic release

is enhanced in parallel. Therefore, in this case, LTD induction does not simply produce pre- and postsynaptic mismatch by decreasing postsynaptic AMPARs, but it does so by triggering also a change in presynaptic strength of the opposite polarity. Such an apparent counterbalancing of synaptic strength between the pre- and the postsynaptic sides is similar to a previous report using guinea pig cortical slices where pairing-induced LTD could be associated with a decrease in quantal amplitude and simultaneous increase in p_r (Sáez and Friedlander, 2009). Given that these studies have been performed either in culture preparations or in brain slices from juvenile animals, it remains to be determined whether the propensity for concurrently expressing synaptic strength changes of the opposite polarity is a feature unique to developing neural networks. In summary, use of optical measurements to study the behavior of single pre- and postsynaptic terminals in a microcircuit could reveal surprising rules of synaptic plasticity with compound features of Hebbian and homeostatic properties that might otherwise be masked by analyzing synapse population.

Future outlook

Synaptic plasticity is an established area of neuroscience research. Nevertheless, it is rapidly evolving as our understanding of the cellular and molecular regulation of synaptic circuits deepens. Here we have focused on durable forms of synaptic plasticity, in particular, on LTP and homeostatic synaptic plasticity mechanisms, the latter having attracted considerable attention in recent years as a form of synaptic modulation that works in concert with Hebbian plasticity. New developments are extending synaptic plasticity research in two directions. On the one hand, super-resolution imaging techniques make it possible to study synapse structure–function relationship at a nanodomain level (Dani et al., 2010; Urban et al., 2011). This will help with gaining insights into, for example, the dynamic relationship between Ca^{2+} channels and synaptic vesicle release sites at the active zone (Holderith et al., 2012), and the organization of postsynaptic receptor scaffolds within the PSD (MacGillavry et al., 2013), both of which are crucial for determining synaptic strength. On the other hand, increasing acknowledgment of the association of synaptic dysfunction with neurological diseases is fueling studies aimed at identifying the synaptic basis for brain disorders using animal models (Sheng et al., 2012; Zoghbi and Bear, 2012). However, there still remain several gaps in our basic understanding of synaptic circuits. Implicit in the problem of how changes in synaptic strength of individual synapses influence each other is the relationship between excitatory and inhibitory synapses that share the postsynaptic neuron (Bannai et al., 2009). Moreover, dendritic protein translation and its regulation by microRNAs permit for exquisite local control of synaptic strength (Cajigas et al., 2010; Siegel et al., 2011). There are also emerging roles in synaptic plasticity for neuron–glia communication and the extracellular matrix that interfaces intercellular interactions (Dityatev et al., 2010; Frischknecht and Gundelfinger, 2012). Cell biology can provide much help in the progress of synaptic plasticity research.

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