The expression of long-term potentiation: reconciling the priests and the postivists

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Long-term potentiation (LTP) of excitatory synaptic transmission in the hippocampus has been investigated in great detail over the past 40 years. Where and how LTP is actually expressed, however, remain controversial issues. Considerable evidence has been offered to support both pre- and postsynaptic contributions to LTP expression. Though it is widely held that postsynaptic expression mechanisms are the primary contributors to LTP expression, evidence for that conclusion is amenable to alternative explanations. Here, we briefly review some key contributions to the ‘locus’ debate and describe data that support a dominant role for presynaptic mechanisms. Recognition of the state-dependency of expression mechanisms, and consideration of the consequences of the spatial relationship between postsynaptic glutamate receptors and presynaptic vesicular release sites, lead to a model that may reconcile views from both sides of the synapse.

1. Introduction

Long-term potentiation (LTP) of excitatory synaptic transmission is a dominant cellular model of learning and memory mechanisms in the vertebrate brain [1] and has been explored in great detail from the time of its original observation in the hippocampus [2]. It is now generally accepted that the induction of LTP at CA3-CA1 synapses in the rodent hippocampus ordinarily requires transient substantial elevation of postsynaptic Ca^{2+} concentration via activation of Ca^{2+}-permeable N-methyl-D-aspartate-type glutamate receptors (NMDARs) and release of Ca^{2+} from internal stores, and the subsequent activation of calcium/calmodulin-dependent protein kinase II (CaMKII) [3–5]. There is less consensus regarding the locus of LTP expression, however, with various observations adduced in support of presynaptic mechanisms such as changes in the mode or probability of vesicular release (reviewed by Lisman & Raghavachari [6]) or of postsynaptic mechanisms such as the insertion or modulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptors (AMPARs) (reviewed by Collingridge et al. [7] and Malinow & Malenka [8]). Just as Alzheimer research has been riven by arguments between Tauists and βaptists [9,10], so has LTP research witnessed zealous disputes between Preists and Postivists. In recent years, postsynaptic models of LTP expression have become widely accepted [1,11], with the authors of one prominent review concluding that there was now ‘conclusive evidence that LTP is mainly expressed postsynaptically’ [12]. Reports of the death of presynaptic expression were exaggerated, however. In this review, we offer a brief and selective overview of some important findings in the history of the expression locus debate and highlight results from our laboratory and others that in our view provide compelling support for the prime importance of presynaptic mechanisms in LTP expression, at least during protein synthesis-independent ‘early’ forms of LTP for which most data are available. We also offer a new model of LTP expression that may help reconcile the different views across the synapse.

2. A history of progress and controversy

Bliss & Lømo [2] were the first to demonstrate long-lasting activity-dependent alterations in synaptic efficacy that had been previously proposed as the neural
substrate of learning and memory [13]. Their initial observations did not, however, establish the relative importance of pre- and postsynaptic mechanisms in the expression of these long-lasting changes [14]. This seemingly innocuous issue has remained at the centre of a scientific controversy that has persisted for 40 years. The following paragraphs offer a brief review of several key findings relevant to this debate.

(a) Increases in presynaptic neurotransmitter release

Skrede & Malthe-Sørenssen [15] were among the first to provide evidence of presynaptic mechanisms in the expression of LTP. They demonstrated that after bursts of electrical stimuli to the Schaffer collaterals in vivo, stimulus-evoked release of D-[3H] aspartate (a proxy for endogenous L-glutamate) in area CA1 was significantly and persistently increased. Shortly thereafter, Dolphin et al. [16] used an in vivo push–pull perfusion technique to demonstrate that mossy fibre (MF) LTP is also associated with a prolonged increase in neurotransmitter release. Increases in extracellular glutamate after LTP have since been corroborated using an assortment of techniques including the induction of LTP in vivo with subsequent monitoring of glutamate levels in slices days later [17], following learning of hippocampus-dependent behavioural tasks [18], as well as through the use of glutamate sensitive electrodes [19]. It should be noted that contrary results have also been reported: neither stimulus-evoked glial glutamate transporter currents [20,21] nor rates of use-dependent pharmacological blockade of glutamate receptor-mediated currents [22,23], both presumed to reflect levels of glutamate in the synaptic cleft, and have been seen to change during LTP, but such changes may have been obscured in these experiments by confounding factors such as experimental duration and simultaneous changes in glial physiology or glutamate receptor kinetics.

More recent evidence for increases in neurotransmitter release during LTP comes from experiments using FM1-43, a fluorescent marker that binds to plasma membranes and is internalized during endocytosis. After such endocytosis and subsequent washout of remaining extracellular dye, residual fluorescence in boutons, as well as its stimulus-evoked disappearance or destaining, reflects the extent of transmitter release [24]. Using this fluorescent marker of presynaptic activity, Siegelbaum and co-workers [25,26] demonstrated that both chemical- and high-frequency stimulation (HFS)-induced LTP at CA1 synapses involve enhanced neurotransmitter release from presynaptic terminals, as indicated by the activity-dependent rate of FM1-43 destaining. Such enhanced destaining was seen following LTP induction via 200 Hz stimulation as well as following a (presumably more physiological) theta-burst induction protocol and was associated with recruitment of additional voltage-gated Ca\(^{2+}\) channels (VGCCs) to terminal boutons [25].

(b) Changes in postsynaptic responsiveness

Although increases in neurotransmitter release provided a potential mechanism for LTP expression at central glutamatergic synapses, increases in the responsiveness of postsynaptic cells to released glutamate offered an alternative explanation. Indeed, evidence for such postsynaptic mechanisms was soon forthcoming. For example, LTP was found to be associated with selective enhancement in AMPAR-mediated responses with no change in NMDAR-mediated responses [27,28], whereas LTP expression via increased glutamate release might be expected to affect evoked responses mediated by both types of glutamate receptors [11]. Such observations led to the hypothesis that functional glutamate receptors newly inserted into the postsynaptic membrane would be sufficient to account for the enhanced synaptic efficacy of LTP [29]. Several independent groups have challenged these findings, however, observing that LTP is associated with changes in both AMPAR- and NMDAR-mediated responses [30–32] or even in some cases with changes only in NMDARs [33]. These discrepancies have not as yet been resolved.

Some of the evidence most persuasively supporting postsynaptic expression of LTP came from studies by Malinow and co-workers [34,35] using green fluorescent protein (GFP)-tagged and electrophysiologically distinctive GluA1-containing AMPARs (GluA1-AMPARs) to monitor AMPAR insertion into dendritic spines during LTP. GluA1-AMPARs display pronounced inward rectification in comparison to GluA2-containing AMPARs, and this rectification signature can be used as a measure of GluA1-AMPAR surface expression [34]. LTP was seen to be associated with an increase in GFP in spines and with a change in the rectification profile of synaptically evoked currents [34,35]. These and related studies provided evidence that AMPARs are inserted into the membrane during NMDA-dependent LTP, and established that such insertion is CaMKII dependent. More recent work from Malinow’s group has further demonstrated that GluA1 AMPAR subunits are inserted into the membrane extrasynaptically and that membrane-bound GluA1-AMPARs are driven into synapses by activity [36]. Neither phosphorylation of GluA1-AMPARs (S845, S831, S818 and S831), GluA1–stargazer interaction, nor the combination of the two is sufficient to cause surface expression at extrasynaptic sites, suggesting that other mechanisms are necessary [37]. While the signalling events by which GluA1-AMPARs are brought to the synapse have not yet been fully elucidated, CaMKII is thought to be a major facilitator. Understanding the exact signalling pathways of AMPAR trafficking during plasticity remains a major focus of LTP research [38]. Notwithstanding recent evidence against necessary participation of GluA1 or GluA2 in LTP [39], in aggregate these data demonstrate the occurrence of postsynaptic receptor-related processes in association with LTP. However, as we outline below, while such processes may indeed be crucial for LTP expression, they do not function by increasing synaptic potency.

(c) Classical quantal analysis

Evidence from early work employing quantal analysis as a means to investigate the locus of LTP expression in the hippocampus [40–42] provided strong evidence that LTP was associated with increases in transmitter release probability \(p\), (based on changes in coefficient of variation (CV) and on decreases in synaptic failure rates) without any corresponding change in quantal size [40,42,43].

Notwithstanding the elegance of these studies, the underlying assumptions of quantal analysis at hippocampal synapses have been called into question: though useful at unitary synapses such as neuromuscular junctions [44], classical quantal analysis may not be an appropriate method of analysis when, as is the case in most studies in hippocampus, evoked responses result from transmission at an unknown number of synapses [45–47]. Furthermore, as noted by
Edwards [48], reduced failure rates can result from postsynaptic rather than presynaptic changes. Synapses with NMDARs but not functional AMPARs in the postsynaptic membrane are ‘silent’, that is, unresponsive to glutamate release at resting membrane potential; insertion of functional AMPARs, for example following an LTP-inducing stimulus, would ‘unsilence’ the synapse making it responsive to presynaptic neurotransmitter release. Such unsilencing provided a plausible alternative explanation for reductions in failure rates following LTP, an explanation supported by the initial results of Kullmann [49] demonstrating a reduction in the CV for AMPAR-mediated responses but no change in either the amplitude of NMDAR-mediated current or the CV for NMDAR responses. Previous observations of selective enhancement of AMPAR-mediated responses associated with LTP without corresponding increase in NMDAR-mediated responses [27,28] were also compatible with this unsilencing explanation, but have not been consistently reproduced [30–32].

Compelling support for the involvement of unsilencing of silent synapses in LTP expression came from studies using a minimal stimulation technique to isolate synapses with NMDA-mediated responses (at positive holding potentials) but no AMPAR-mediated responses (at negative holding potentials). Using this method, Liao et al. [50] demonstrated that AMPAR-mediated responses could be detected after LTP at synapses previously lacking such responses (i.e. NMDAR-only synapses) in parallel with reductions in synaptic failure rates. Similar results were independently obtained by Isaac et al. [51] around the same time. Both groups, however, worked with hippocampal slices from juvenile rats at ages (less than or equal to 20 postnatal days) when postsynaptically silent synapses are particularly abundant [52]. This raises the question whether LTP expression via synapse unsilencing is a developmentally restricted phenomenon. We will return to this question shortly, but the disagreement surrounding the interpretation of classical quantal analysis indicated that a less ambiguous form of quantal analysis could help to resolve the roles of pre- and postsynaptic mechanisms in LTP expression [48].

(d) Optical quantal analysis

Criticisms of classical quantal analysis at hippocampal synapses have focused on the inability to resolve single unitary synaptic responses [45]. Optical detection of synaptically evoked postsynaptic Ca$^{2+}$ transients (EPSCaTs) within single dendritic spines [53–55] has given us a means to overcome this difficulty. EPSCaTs are mediated by Ca$^{2+}$ entry through NMDARs, amplified by Ca$^{2+}$ release from internal stores [53]. To monitor EPSCaTs, a cell is impaled, loaded with fluorescent Ca$^{2+}$ indicator, excitatory postsynaptic potentials (EPSPs) are evoked via extracellular stimulating electrode, and the dendritic tree is scanned for spines that display a fluorescence change in response to stimulation. Simultaneous monitoring of somatically recorded EPSPs and EPSCaTs in the spine permits optical quantal analysis [56,57], whereby quantal parameters of transmission can be determined at individual synapses without the interpretation difficulties of classical methods. In particular, as EPSCaTs are reliable indicators of transmission at the imaged synapse [53–55,58], the probability of a presynaptic action potential generating EPSCaTs in a postsynaptic spine provides an accurate estimate of $p_r$ at the corresponding presynaptic terminal. Using this approach, our initial optical quantal analyses at the same synapses before and after LTP induction revealed presynaptic contributions to LTP expression both at MF synapses [57] as well as at associational and Schaffer collateral synapses on CA3 and CA1 neurons [56]. Whereas it is widely accepted that LTP at MF synapses is associated with an increase in neurotransmitter release [59], this indication that $p_r$ increases with LTP at Schaffer-associational synapses, though consistent with earlier classical quantal analyses [40,42,60], was at odds with the evidence for postsynaptic expression described above, raising questions about the relative importance of these pre- and postsynaptic expression mechanisms, and about how they might relate.

Subsequently, we employed a subtractive procedure that allowed us to address these questions by establishing the contribution of the EPSCaT-generating synapse to the simultaneous somatically recorded polysynaptic EPSP, and thus to determine the unitary EPSP due to the imaged synapse. The results from Enoki et al. [58] were clear: LTP at Schaffer-associational synapses, whether induced by HFS or by pairing synaptic activation with postsynaptic depolarization, is associated with an increase in synaptic reliability (fewer failures, i.e. increased $p_r$) with no change in synaptic potency (unitary EPSP amplitude). The same results were obtained without subtraction in the rare cases where ‘minimal stimulation’ actually activated only one synapse; in those cases, EPSCaTs occurred in constant conjunction with EPSPs, and EPSCaT failures were in constant conjunction with EPSP failures, confirming that EPSCaTs are a reliable measure of neurotransmitter release. These experiments were carried out on hippocampal slices of young adult (≥P21) rats to reduce the prevalence of silent synapses [12,52,61], for reasons that will be made clear in the next section. Our optical quantal analyses refine and reinforce the conclusions of the earlier classical quantal analyses cited above and indicate not only that LTP at active hippocampal associational synapses is associated with increased probability of neurotransmitter release, but also that, at least under the usual conditions by which LTP is induced, such enhanced reliability is the principal means by which LTP is expressed.

(e) State-dependent long-term potentiation

As noted above, observations of synaptic unsilencing in LTP raised the question of whether this phenomenon is of general importance or is developmentally restricted. We addressed this question via optical quantal analysis and found differential state-dependent expression mechanisms for LTP at silent versus active synapses [62]; LTP at silent synapses proceeds via unsilencing, in keeping with previous reports. Postsynaptic dialysis with an inhibitor of vesicular fusion prevented unsilencing at these synapses, consistent with the notion that insertion of receptors in the postsynaptic membrane is essential for LTP expression by such unsilencing. Importantly, no changes in $p_r$, as inferred from EPSCaTs failure rates, were detected when LTP was expressed at silent synapses observed during Mg$^{2+}$-free superfusion or postsynaptic depolarization. After unsilencing, however, those same synapses displayed significant increases in $p_r$ following a second round of LTP induction [62]. Overall, these studies indicate that unsilencing by postsynaptic molecular insertion involving vesicular fusion is the main mechanism for LTP expression at silent synapses, whereas an increase in $p_r$ is the primary mechanism for LTP expression at synapses once they have been unsilenced.
Figure 1. A simplified model of the expression of NMDA-dependent LTP at CA1 associational/commissural synapses. (a,b) Postsynaptic expression mechanisms are responsible for LTP at silent synapses. (a) Transmission fails at silent synapses prevalent in immature CA1, as any postsynaptic AMPARs are too far from the active zone to encounter activating concentrations of released glutamate (shading in synaptic cleft), while NMDARs, though suitably localized, are blocked by Mg$^{2+}$ at normal resting potentials. (b) Following an LTP-inducing stimulus, Ca$^{2+}$ enters the postsynaptic cell and activates CaMKII, mediating extrasynaptic insertion of GluA1-AMPAR/stargazin which then diffuses into the synaptic membrane. Stargazin mediates synaptic trapping of the AMPAR by binding to vacant PSD-95 PDZ1/2 domains (slots) close to the active zone. Additional GluA1-AMPARs inserted at extrasynaptic sites cannot detect glutamate released in the defect. Synaptic GluA1-AMPARs are subsequently exchanged for GluA2-containing AMPARs. (c) Presynaptic expression mechanisms are responsible for LTP at active synapses. Following an LTP-inducing stimulus, new PSD-95 is added to the edges of the postsynaptic density (PSD), making available new slots for GluA recruitment. GluA1-AMPARs inserted extrasynaptically diffuse laterally to these slots, but are too far from the vesicular fusion site at the presynaptic active zone to be activated by released glutamate. These GluA1-AMPARs can also exchange with GluA2-AMPARs in the PSD closer to the active zone; such exchange can alter rectification properties of synaptic currents, but will have little effect on EPSP amplitude. New GluA1-AMPARs are also recruited to replenish extrasynaptic sites. Surface adhesion molecules (SAMs) recruited to slots in the new synaptic PSD-95 recruit binding partners in the presynaptic membrane, in turn triggering an increase in the probability of neurotransmitter release by mechanisms that may include (i) increased spatial coupling of VGCCs to release machinery, (ii) increased number of docked/primed vesicles and (iii) recruitment of new VGCCs to the presynaptic membrane, as well as increased Ca$^{2+}$ sensitivity of the vesicular release machinery, change from partial to full vesicular fusion, and various other mechanisms not shown.
(f) Synaptic scaffolding proteins

The scaffolding protein PSD-95 has been implicated in AMPAR insertion during LTP, principally through its interactions with the transmembrane AMPAR regulatory protein (TARP) stargazin [63,64]. PSD-95 contains three consecutive PDZ domains in its N-terminal region that act as ‘slots’ capable of binding various transmembrane proteins including certain ion channels and surface adhesion molecules (SAMs) and anchoring them at synaptic sites [65]. Such binding of stargazin via its C-terminal domain to a PDZ domain of PSD-95 or related proteins appears to be crucial for AMPAR targeting to the synapse [66,67]. PSD-95 is capable of dimerization and multimerization at postsynaptic sites through N-terminal interactions [68] and has been implicated in synapse maturation through clustering [69,70]. This scaffolding protein could thus plausibly mediate changes in synaptic efficacy by recruiting assemblies of proteins required for synaptic transmission. Indeed, overexpression of PSD-95 has been shown to mimic aspects of LTP, increasing both the amplitude and frequency of AMPA-mediated miniature excitatory postsynaptic currents (mEPSCs) [70–72]; an increase in the frequency of mEPSCs is commonly correlated with increases in $p$. Both GluA1-containing AMPARs and synaptophysin levels increase following overexpression of PSD-95, as indicated by immunostaining [70]. Conversely, knockdown of PSD-95 decreases synaptic strength and prevents the developmental accumulation of functional AMPARs at synaptic sites [73]. Of particular interest, stability of PSD-95 at the postsynaptic density (PSD) appears to be modulated by interaction involving its TARP-binding PDZ domains [74], which may account for certain requirements for GluA1 in LTP expression [75].

3. Reconciliation: one model for both sides

The following simple unifying model of LTP expression emerges from consideration of results such as those summarized above.

(a) Silent synapses: postsynaptic expression

Silent glutamatergic synapses, abundant early in development, have postsynaptic elements that express NMDARs without functional AMPARs (figure 1a), and are thus unresponsive to evoked glutamate release at normal resting membrane potentials. LTP-inducing stimuli, possibly by activating CaMKII, trigger the extrasynaptic insertion of GluA1-containing AMPARs into the postsynaptic membrane (figure 1b). Complexed with stargazin, they can diffuse laterally to synaptic sites where they are anchored when stargazin binds to vacant PDZ domains in subsynaptic PSD-95 [63,76]. Such GluA1-AMPARs at synaptic sites can now respond to evoked vesicular release of glutamate, yielding observed increases in AMPAR currents and rectification changes as well as decreases in synaptic failures rates. Synaptic GluA1-containing AMPARs may thereafter be exchanged for GluA2-heteromeric AMPARs [77]. The unsilencing of a silent synapse is also expected to reduce the threshold for subsequent LTP at that synapse by enabling AMPAR-induced partial depolarization, and thus relaxing the requirements of coincident nearby synapse activation or dendritic regenerative depolarization for removal of magnesium block from NMDARs. It should be noted that transiently expressed homomeric GluA1-AMPARs (unlike GluA2-containing AMPARs) are Ca$^{2+}$-permeable and that the additional Ca$^{2+}$ influx is thought to contribute to the stability of LTP [77]. In any case, LTP at silent synapses appears to rely largely on postsynaptic expression mechanisms.

(b) Active synapses: presynaptic expression

In contrast to silent synapses, postsynaptic elements at active, non-silent synapses already contain functional AMPARs and are thus responsive to evoked glutamate release at normal resting membrane potentials. We posit that unsilencing of synapses permits subsequent LTP-induced aggregation of PSD-95 molecules at the PSD. This clustering of PSD-95 adds new empty slots for receptors, ion channels and SAMs to be inserted into the plasma membrane. These new slots are central to the different way in which LTP is expressed at active, non-silent synapses. Thus LTP induction at active synapses leads not only to extrasynaptic insertion of GluA1-containing AMPARs into the postsynaptic membrane, as was the case at silent synapses, but also to addition of new PSD-95 family proteins to the PSD. The newly inserted GluA1-containing AMPARs diffuse laterally until they are captured by vacant PDZ domains (slots) of the newly added PSD-95.

We have shown that individual synapses can sustain multiple episodes of potentiation [58], and we suggest that most mature synapses, which carry the majority of synaptic weight, will have been multiply potentiated. PSD-95 forms a highly structured lattice at the PSD [78], and it is likely that net addition of new PSD-95 can only occur at the edges of the PSD. Most mature Schaffer collateral–commissural synapses have PSDs with diameter more than 250 nm [79], and AMPARs are preferentially distributed at the periphery of the PSD [80,81]. We propose that AMPAR-binding PDZ domains of PSD-95 present at PSDs in mature synapses under baseline conditions tend already to be filled as a consequence of earlier potentiation events. In response to new potentiating stimuli, net addition of newly inserted AMPARs therefore can only occur where new PSD-95 is added to the edges of the PSD. AMPARs, however, bind glutamate with relatively low, millimolar, affinity. Peak glutamate concentrations in the synaptic cleft may reach millimolar levels, but such levels are achieved only very close in space and time to the point of vesicular opening; from there, glutamate concentration decays rapidly within milliseconds and hundreds of nanometres. Considerations of glutamate release, kinetics of binding to AMPARs, diffusion in the cleft and uptake [82] indicate that the AMPARs activated by evoked glutamate release are mainly those within a small ‘hotspot’ of diameter 250 nm or less, centred opposite the release site [83]. Thus, potentiation at mature synapses would involve addition of AMPARs that will, in the main, be too far from the release site to be significantly activated, at least at low stimulus frequencies under normal physiological conditions: addition of new AMPARs would make little contribution to the functional potentiation of mature synapses. Such AMPARs, newly inserted in the extrasynaptic membrane can, however, exchange with AMPARs already in the central ‘hotspot’ region of the PSD, or diffuse into slots vacated by GluA2-containing AMPARs undergoing constitutive recycling (84); figure 1c). Such exchange would lead to observed changes in biophysical characteristics including rectification properties of excitatory postsynaptic currents (EPSCs). However, as the total number of AMPARs contributing to
those evoked currents remains constant, such exchange would have only minor effects on EPSC or EPSP amplitude.

There are, of course, many synapses with smaller PSDs, where AMPARs added to the margin could be within the ‘hotspot’ of sensible glutamate release. Such small synapses, however, appear to contribute little to the aggregate EPSP at the soma and initial segment [58]; we are concerned here with the larger, stronger synapses that are the main contributors to intracellularly recorded EPSPs and observed LTP.

Whereas LTP at active synapses thus has little effect on synaptic potency, increases in synaptic reliability are proportional to the increases in synaptic strength and sufficient to account for them [58]. How do these presynaptic changes arise? As noted above, LTP that is induced by postsynaptic Ca2+ elevation but expressed by changes in the reliability of evoked transmitter release requires retrograde signalling across the synapse. Identifying the molecular basis of such retrograde signalling is now a key challenge. Although our model is consistent with various diffusible molecules that have been suggested as signals [85], it is particularly compatible with such a signalling role for SAMs: recruited to the PSD by newly added PSD-95, postsynaptic SAMs could in turn recruit their presynaptic binding partners. SAM recruitment could contribute to maintaining the proportionate size of active zones and postsynaptic densities at presumptive glutamatergic synapses [86,87]. Transsynaptic binding, with consequent dimerization or higher aggregation of presynaptic SAMs, could then trigger an increase in p, by a variety of mechanisms including, but not limited to, increased spatial coupling of VGCCs to the synaptic release machinery, increased number of docked/primed vesicles, recruitment of new VGCCs (i, ii and iii, respectively, in figure 1c), increased Ca2+ sensitivity of the vesicular release machinery and change from partial to full vesicular fusion.

We close by noting that our model deals specifically with expression of potentiation during its early, protein synthesis-independent phase. Whether it is also relevant to expression of late, protein synthesis-dependent potentiation remains to be determined. We would be surprised if presynaptic mechanisms responsible for the majority of early LTP expression turn out to be entirely replaced by alternative postsynaptic mechanisms yielding similar levels of potentiation during late LTP expression. A requirement for postsynaptic protein synthesis would not be inconsistent with this position if, for example, synthesis of new postsynaptic scaffold proteins is essential to consolidate the transsynaptic signalling essential for maintained presynaptic expression. It will be important to determine precisely how, and how much, these or other mechanisms contribute to the modulation of synaptic reliability in LTP and other forms of long-lasting plasticity that underlie memory and its disorders.

References


