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Homeostatic signaling: the positive side of negative feedback

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Synaptic homeostasis provides a means for neurons and circuits to maintain stable function in the face of perturbations such as developmental or activity-dependent changes in synapse number or strength. These forms of plasticity are thought to utilize negative feedback signaling to sense some aspect of activity, compare this with an internal set point, and then adjust synaptic properties to keep activity close to this set point. However, the molecular identity of these signaling components has not been firmly established. Recent work suggests that there are likely to be multiple forms of synaptic homeostasis, mediated by distinct signaling pathways and with distinct expression mechanisms. These include presynaptic forms that depend on retrograde signaling to presynaptic Ca^{2+} channels, and postsynaptic forms influenced by BDNF, TNFα and Arc signaling. Current challenges include matching signaling elements to their functions (i.e. as detectors of activity, as part of the set-point mechanism and/or as effectors of synaptic change), and fitting these molecular candidates into a unified view of the signaling pathways that underlie synaptic homeostasis.

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Introduction

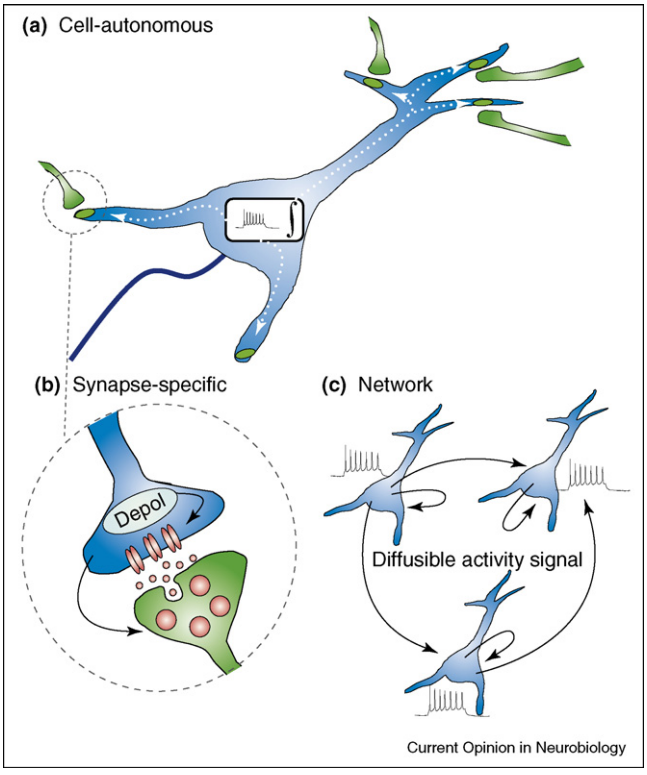
Homeostatic synaptic plasticity is emerging as an important complement to Hebbian forms of plasticity in the activity-dependent refinement of synaptic connectivity [1–3]. Loosely defined, a 'homeostatic' form of plasticity is one that acts to stabilize the activity of a neuron or neuronal circuit in the face of perturbations, such as changes in cell size or in synapse number or strength, that alter excitability. In the past decade, a growing number of plasticity phenomena have been identified in a wide range of systems that conform to this definition of homeostatic plasticity [4–6]. Generating and maintaining stability in neuronal circuit function is likely to be so fundamentally important that circuits employ multiple overlapping (and perhaps partially redundant) mechanisms that cooperate to constrain excitability. These mechanisms include: activity-dependent regulation of intrinsic neuronal firing properties [4,5]; presynaptic and postsynaptic forms of excitatory synaptic plasticity, such as synaptic scaling, that adjust the strength of all excitatory synapses of a neuron up or down to stabilize firing [1,2]; balancing of excitation and inhibition within complex recurrently connected neuronal networks [7,8]; and compensatory changes in synapse number [9,10•]. Importantly, several studies have shown that these compensatory changes in synaptic and neuronal properties act to restore neuronal firing rates to control levels following perturbations [11,12], indicating that these mechanisms are truly 'homeostatic' in nature, and act to conserve some aspect of neuronal firing.

The existence of homeostatic plasticity in a variety of systems is well established, but little is known about the underlying signaling mechanisms. To implement homeostatic plasticity, neurons must be able to sense some aspect of activity, possibly integrate this measure over time, compare this (integrated) signal with a set-point value, and adjust synaptic properties to minimize the difference between actual activity and this set point. Such negative feedback is a fundamental feature of many physiological systems [1,13], but how it is implemented in synaptic homeostasis is currently unknown. Understanding the molecular underpinnings of these homeostatic signaling loops is likely to be of major importance in understanding the processes that underlie activity-dependent refinement of neuronal circuitry, and also disease states and developmental disorders in which the balance between excitation and inhibition is disrupted. At the moment we are far from understanding the complete signaling pathways that underlie any form of synaptic homeostasis. Important open questions include: the nature of the 'activity' signal; the molecular identity of the 'integrator'; whether synaptic homeostasis is cell-autonomous or requires altered function of entire networks; and whether synaptic homeostasis operates locally (in a synapse-specific manner) or globally on all synapses of a neuron (Figure 1). In this review, I focus on several forms of synaptic homeostasis, and discuss findings from the past two years that are beginning to shed light on these outstanding questions.

Rapid homeostatic signaling at the NMJ

One of the best-described examples of synaptic homeostasis occurs at the neuromuscular junction (NMJ), where perturbations in presynaptic function lead to compensatory changes in postsynaptic excitability, and vice versa

Figure 1



Three different models for how synaptic homeostasis could be implemented. **(a)** Cell-autonomous synaptic homeostasis. In this model, individual neurons sense their own activity (possibly by sensing depolarization-induced changes in Ca^{2+} influx), integrate this measure of activity over some time step, and then adjust all of their synaptic weights up or down to keep this value relatively constant. **(b)** Alternatively, synaptic homeostasis could be implemented in a synapse-specific manner, in which local synaptic signaling induces compensatory changes in presynaptic and/or postsynaptic function. For example, local glutamate receptor activation that causes depolarization (Depol) might negatively regulate abundance of glutamate receptors on the postsynaptic cell (blue) and also generate a retrograde signal that negatively regulates vesicle release from the presynaptic terminal (green). **(c)** Finally, changes in network activity could lead to altered release and build-up of a diffusible 'activity signal' that then negatively regulates synaptic function.

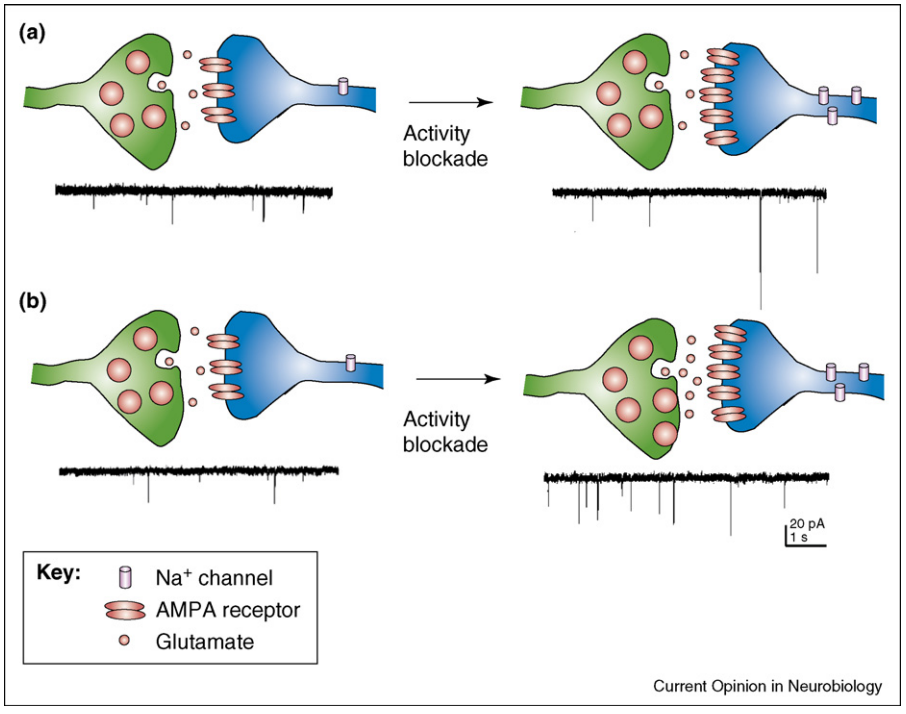
[1,14]. These changes compensate precisely for altered function, so that neuromuscular transmission is maintained. This has led to the idea that during development nerve excitation keeps up with muscle growth through homeostatic compensatory changes in synaptic transmission. The majority of work at the NMJ has focused on compensatory increases in presynaptic neurotransmitter release induced by a reduction in postsynaptic muscle excitation. In *Drosophila*, genetic reductions in glutamate receptor function or chronic hyperpolarization of the muscle lead to compensatory increases in transmitter release, and the relevant activity signal was thought to be chronic (days long) changes in muscle depolarization [15].

A recent study [16•] has forced a major revision to this model by presenting three new lines of evidence. First, it showed that increased transmitter release can be induced within 10 min of pharmacological blockade of glutamate receptors on the postsynaptic muscle — far faster than had previously been appreciated using genetic manipulations, and much faster than homeostatic compensation at CNS synapses (which requires at least several hours to become detectible [11,17•]). Second, large changes in depolarization were not required; rather, homeostatic compensation occurred in response to subtle changes in the amplitude of excitatory postsynaptic potentials (mEPSPs, the response to individual vesicles of glutamate) [16•]. Finally, impaired function of a presynaptic Ca^{2+} channel blocked this form of synaptic homeostasis, confirming the requirement for a retrograde or transsynaptic signal from the postsynaptic muscle to the presynaptic terminal. Whether a change in mEPSP amplitude is signaled to the postsynaptic muscle by changing local Ca^{2+} signaling, or through some other means, is unknown. The retrograde signal has not yet been identified, and on the presynaptic side it is not clear what role the Ca^{2+} channel target has in enhancing transmitter release. The *Drosophila* NMJ is a highly tractable system for working out the details of signaling pathways, so progress in answering these questions is likely to be made quickly. It will be very interesting to determine the precise functional role of this rapid presynaptic homeostasis, and whether similar rapid forms of synaptic homeostasis occur at the mammalian NMJ and/or at central synapses.

Synaptic homeostasis in the vertebrate CNS

Homeostatic synaptic compensation could occur through a variety of presynaptic and postsynaptic changes, acting either in isolation or synergistically. How synaptic homeostasis is implemented has important consequences for circuit function: for example, presynaptic changes in release probability will strongly affect short-term plasticity and thus information transfer across the synapses, whereas postsynaptic changes in receptor number will tend to scale up or scale down postsynaptic responsiveness without affecting the short-term dynamics of synaptic transmission [3]. The first reports of synaptic homeostasis at central synapses suggested that central neurons respond to changes in activity by scaling up or down the strength of all of their synapses through a simple change in the accumulation of postsynaptic glutamate receptors [11,18,19], with no perceptible changes in presynaptic function (Figure 2a). For example, treatment of neocortical cultures with tetrodotoxin (TTX) increased the amplitude but not the frequency of miniature excitatory postsynaptic currents (mEPSCs), and subsequent studies found no changes in release probability, synapse number or short-term plasticity [11,20]. By contrast, several other *in vitro* studies (using hippocampal preparations) have reported that activity deprivation

Figure 2



Expression loci of synaptic homeostasis at central synapses. At neocortical and hippocampal excitatory synapses onto principle neurons, the expression mechanisms of synaptic homeostasis change with time *in vitro*. **(a)** For neurons <2.5 weeks *in vitro*, activity deprivation scales up excitatory synaptic strengths through postsynaptic changes in receptor accumulation, without perceptible changes in presynaptic function [10•,20]. Traces illustrate mEPSCs before and after activity blockade; the amplitude but not the frequency of mEPSCs is increased. There are also changes in the postsynaptic boosting of synaptic inputs by Na^+ channels [10•]. **(b)** By contrast, for neurons >2.5 weeks *in vitro*, activity blockade produces a more complex set of changes. In addition to the postsynaptic changes in (a), there are now recruited an additional set of presynaptic changes; these possibly include increased glutamate packaging into vesicles, an increase in the number of functional release sites and an increase in vesicle release probability. Traces illustrate mEPSCs before and after activity blockade; now both amplitude and frequency of mEPSCs is increased.

induces changes in presynaptic release probability and number of release sites (Figure 2b) [12,21–23]. Until recently, it was unclear whether these contradictory findings were due to differences in culture preparations or conditions, differences in mode of activity deprivation, or some other factor. A recent study [10•] has shed light on this issue by testing the response of cortical and hippocampal neurons to the same activity deprivation paradigm (2 d of TTX treatment) after different periods of time *in vitro*. The same neurons had a purely postsynaptic response to activity deprivation <2.5 weeks *in vitro*, but >3 weeks *in vitro* they had a mixed presynaptic and postsynaptic response, in which quantal amplitude, release probability and synapse number were all increased in parallel (Figure 2) [10•]. It remains unclear why this transition occurs, and whether it represents an artifact of prolonged exposure to the *in vitro* environment or a response of younger versus more mature central synapses to the same deprivation paradigm. Whichever of these proves to be the case, this study strongly suggests that there are several distinct homeostatic processes at central synapses that can be separately engaged by activity deprivation, and that probably involve different signaling pathways. I will now discuss in turn what is currently known about the signaling pathways involved in the presynaptic and postsynaptic forms of homeostatic mechanisms at central synapses.

Presynaptic homeostatic plasticity at central synapses

As I have already discussed, activity-deprivation in older neuronal cultures increases mEPSC frequency, presynaptic vesicle recycling and vesicle release probability during evoked synaptic transmission (inferred from FM-dye destaining rates) [10•,12,21,22]. These studies suggest that under some circumstances, chronic inactivity at central synapses, as at the NMJ, can increase release probability and the number of functional release sites. Most studies that have looked have found that these presynaptic changes are also accompanied by an increase in mEPSC amplitude [10•,22,23]. This has been ascribed to changes in postsynaptic receptor accumulation, and such changes are well documented (see the following section). However, several recent studies suggest that

there is an additional presynaptic component to changes in quantal amplitude. Chronic activity blockade in cortical cultures increases the expression of vesicular glutamate transporter (VGLUT)1, whereas hyperactivity reduces VGLUT expression [24,25]. Because changes in VGLUT levels can modify quantal size, presumably by altering the amount of glutamate packaged into each vesicle [26,27], these data suggest that changes in postsynaptic glutamate receptor number and in presynaptic glutamate receptor packaging cooperate to regulate quantal size homeostatically.

Currently, little is known about the signaling mechanisms that regulate presynaptic homeostasis at central synapses. Chronic hyperpolarization of the postsynaptic neuron can induce an increase in mEPSC frequency, suggesting that the relevant activity signal for these presynaptic changes is postsynaptic depolarization [12], but it is not clear whether local dendritic depolarization or prevention of postsynaptic firing is the crucial factor. Inactivity and the resulting hyperpolarization triggers at least some aspects of presynaptic homeostatic plasticity through changes in Ca^{2+} influx through L-type Ca^{2+} channels [22] but, because these experiments utilized bath-applied channel blockers, it has not been established whether this is due to blockade of presynaptic or postsynaptic Ca^{2+} channels.

The sufficiency of postsynaptic hyperpolarization to trigger presynaptic changes raises the possibility that retrograde or transsynaptic signaling of some sort is important for presynaptic homeostasis of central synapses, just as at the NMJ. Alternatively, chronic inactivity for many (>3) days increases synapse size [21], raising the interesting possibility that, rather than a classic retrograde signaling mechanism, postsynaptic growth (which would increase the area available for tethering glutamate receptors) might trigger a coordinated expansion of the presynaptic terminal (along with the presynaptic release machinery). This model is appealingly simple, but does not account for the more rapid (within 4–12 h) homeostatic changes in mEPSC amplitude that have been observed well before there are observable changes in synapse size [11,17•]; nor does it explain how postsynaptic changes can occur independently of presynaptic changes [10•,20].

Signaling mechanisms that underlie synaptic scaling

Expression mechanisms of synaptic scaling

Most studies of homeostatic plasticity in central neurons have observed that pharmacological manipulations of activity induce bidirectional compensatory changes in mEPSC amplitude at glutamatergic synapses [2]. These changes in quantal amplitude seem to operate uniformly on the entire distribution of synaptic weights, in effect scaling synaptic strength up or down; hence the origin of the term 'synaptic scaling' [11]. Synaptic scaling has been observed at cortical synapses following *in vivo* sensory deprivation and is developmentally regulated, suggesting that it is important in regulating cortical excitability during activity-dependent development [7,28,29]. The expression mechanisms of synaptic scaling are reasonably well understood. Changes in activity lead to bidirectional changes in the accumulation of AMPA receptors [11,18–20], and these changes are sufficiently large to account for the majority of the effect on mEPSC amplitude (but see the prior section on regulation of VGLUT levels). Less consistent are findings on the subunit composition of the newly accumulated receptors: in spinal and neocortical neurons, there are proportional changes in GluR1 and GluR2 subunits of the AMPA-type glutamate receptor [18,20], whereas several studies on hippocampal neurons have reported enhanced GluR1 accumulation but smaller or absent changes in GluR2 [17•,22,30]. This might represent real differences in the trafficking rules for glutamate receptors in these different cell types, or a methodological difference between studies (such as method of activity block). At cortical synapses <3 weeks *in vitro*, it has been shown that these changes in quantal amplitude translate into changes in evoked transmission; interestingly, the increase in evoked transmission is larger than the effect on mEPSCs, but not because of changes in quantal content. Rather, there is an increase in the boosting of synaptic potentials by dendritic Na^+ channels, suggesting that Na^+ channel accumulation in the dendrites is also increased in concert with changes in AMPA receptors, and that the Na^+ channels act synergistically with AMPA receptors to increase evoked synaptic transmission [20]. This suggests that activity-deprivation could induce additional unexplored changes in cellular processes that depend on dendritic Na^+ channels, such as synaptic integration and the ability of spikes to propagate backwards into dendrites.

Induction requirements for synaptic scaling

Attempts to understand the signaling pathways involved in synaptic scaling have focused on the role of various candidates in homeostatic AMPA receptor trafficking. To date, all *in vitro* studies have induced synaptic scaling using global pharmacological manipulations — generally either TTX or glutamate receptor blockers — so it is currently unknown whether the relevant activity signal for synaptic scaling is postsynaptic changes in firing, presynaptic changes in release, or local dendritic changes in receptor activation and/or Ca^{2+} influx. Whereas blockade of NMDA receptors alone does not induce synaptic scaling, a recent study [17•] showed that in the presence of bath-applied TTX, local blockade of NMDA receptors could accelerate synaptic scaling at the site of block. This suggests that there is local regulation of the speed of synaptic scaling, but that this mechanism operates only when a global scaling process has been initiated. Understanding the mechanisms and functions of synaptic scaling will depend on working out the precise activity requirements for its induction.

Activity signals for synaptic scaling

A second crucial issue is how changes in activity are signaled to neurons or synapses. Several activity-dependent molecular signals have been proposed to have a role in synaptic scaling, including brain-derived neurotrophic factor (BDNF), cytokine tumor-necrosis factor α (TNFα) and the effector immediate-early gene product Arc. In cortical cultures, chronic BDNF treatment on its own has no effect on mEPSC amplitude but can overcome the effects of activity deprivation, and preventing activation of endogenous BDNF receptors mimics the effects of activity blockade. This suggests that activity-dependent release of BDNF is an important activity signal in synaptic scaling. However, in some studies BDNF has been reported to enhance mEPSC amplitude onto excitatory neurons [31,32], suggesting that the effects of chronic BDNF depend on brain region or developmental stage. These experiments employed bath-applied BDNF (which is highly non-physiological), and evaluating the role of BDNF more precisely will require manipulations that can better mimic endogenous activity-dependent release and action. Recently it was shown in hippocampal cultures that bath application of TNFα rapidly increases mEPSC amplitude and surface AMPA receptor number [33], and that conditioned medium from cultures treated for 2 d with TTX increased mEPSC amplitude through a TNFα-dependent mechanism [34•]. Further, this study made the interesting observation that the TNFα originated from glia rather than neurons. This indicates that TNFα-mediated synaptic scaling is not cell-autonomous, and instead suggests that network-wide changes in activity increase or decrease the amount of TNFα released from glia, which then regulates surface AMPA receptors on neurons in a network-level homeostatic process.

Complicating matters still further, two recent papers [35•,36•] have suggested that activity-dependent expression of Arc is necessary and sufficient to account for synaptic scaling. In cultured neurons, Arc levels are increased and decreased by the chronic changes in activity that are used to induce synaptic scaling, and overexpression of Arc decreases AMPA-receptor-mediated currents and prevents the increase in mEPSC amplitude induced by chronic TTX; conversely, knockdown of Arc elevates AMPA-receptor-mediated transmission and occludes the effects of TTX on mEPSCs [36•]. The effects of Arc seem to be mediated through endocytosis of AMPA receptors [37], although there is disagreement on which subunits — GluR1 or GluR2/3 — are targeted [35•,36•]. These studies suggest that strong synaptic stimuli that activate strong Arc expression will result in a reduction in surface AMPA receptor number, thus producing a 'homeostatic' reduction in synaptic strength. Because Arc expression can be induced *in vivo* in a cell-autonomous way [38,39], this Arc-mediated plasticity, in contrast to TNFα-mediated plasticity, is likely to be cell-autonomous. However, there are a few caveats to these studies. First, although Arc knockdown increased synaptic transmission in cultured neurons and slice preparations [35•,36•], hippocampal basal synaptic transmission in slices from *Arc* knockout mice is normal [40], and the reason for the discrepancy between studies is not clear. A second caveat is that the effects of Arc overexpression are reported to be weak in high-density cortical cultures [36•], yet such cultures show a robust reduction in mEPSC amplitude in response to elevated activity [11]. A final unanswered question is whether Arc expression *in vivo* is a graded function of neuronal activity, or whether Arc is induced only following strong stimuli. If strong stimuli are required, then this pathway could be engaged only following extreme stimuli such as seizures, and therefore it could not account for the precise and graded reductions in synaptic strength as a function of small changes in depolarization that have been observed in some synaptic scaling paradigms [41].

It is currently difficult to fit the aforementioned findings into a unified view of the molecular pathways involved in synaptic scaling. High levels of BDNF can induce Arc expression [42–44], suggesting one possible link between these two pathways, but whether this pathway is activated in response to physiological changes in activity is not known. Whether BDNF, TNFα and Arc prove to be part of the core signaling pathway for synaptic scaling, or are eventually demoted to the status of modulators of synaptic function and the synaptic scaling machinery, remains to be seen. For example, Arc overexpression and complete knockout are extreme manipulations that disrupt the normal constitutive recycling of AMPA receptors. If synaptic scaling independently targets elements of the constitutive recycling pathway, then disrupting this pathway would prevent the normal expression of synaptic scaling. Similarly, the TNFα data are in some respects difficult to reconcile with other studies of synaptic scaling [45]. In particular, synaptic scaling is a graded process in which the magnitude of synaptic change is fairly linearly related to the length of the deprivation, and changes are already apparent after as little as 12 h of TTX treatment [11]. By contrast, conditioned medium from TTX-treated cultures had no effect on synaptic strength until 48 h [34•], suggesting that TNFα is released from glia in significant amounts only following prolonged periods of inactivity. The TNFα pathway might thus be required for the maintenance of synaptic scaling during prolonged periods of inactivity, rather than for its initial induction [45]. These considerations raise the sobering possibility that each of these signaling pathways (BDNF, glial-derived TNFα and Arc) act independently to induce functionally distinct forms of synaptic plasticity.

Conclusions

The field of homeostatic plasticity is still young, and there are currently more questions about the induction

mechanisms and signaling loops involved than there are answers. The field is in a period of almost exponential growth, and it is likely that additional phenomenology, as well as numerous molecular players, will rapidly accumulate over the next few years. A thoughtful approach to a few central challenges in the field will, in my view, greatly aid progress. First, given the wide range of phenomena that are currently sheltering under the 'homeostatic' umbrella, it is crucial to determine which form is under study, because the mechanisms will clearly differ: compare, for example, what is known about rapid presynaptic homeostasis at the NMJ with what is known about synaptic scaling. Second, several of the molecular players linked to synaptic homeostasis (notably Arc and BDNF) also influence other forms of plasticity, such as long-term potentiation (LTP), long-term depression (LTD) and inhibitory and intrinsic plasticity [35•,46–50]. In some cases, this is likely to reflect a convergence of multiple plasticity pathways onto the same molecular effectors, but in other cases it might be that a change in synaptic function induced by one plasticity mechanism has indirect effects on the expression of others. A final and related point is that it will be essential to differentiate modulators of synaptic homeostasis from core mediators. A glance through the LTP literature suggests that this is no easy task and, as the number of molecules implicated in synaptic homeostasis proliferates, things are likely to get murkier before the dawn.

Acknowledgements

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