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Dendritic signalling and homeostatic adaptation

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Homeostatic plasticity mechanisms are employed by neurons to alter membrane excitability and synaptic strength to adapt to changes in network activity. Recent studies suggest that homeostatic processes can occur not only on a global scale but also within specific neuronal subcompartments, involving a wide range of molecules and signalling pathways. Here, we review new findings into homeostatic adaptation within dendrites and discuss potential signalling components and mechanisms that may mediate this local form of regulation.

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Introduction

Anatomical studies have revealed that neurons in the central nervous system display diverse morphologies [1]. Different cell types can often be readily identified by the arborisation pattern of a subcompartment of the neuron known as the dendritic tree. Dendrites are the extensive processes that project from the soma of neurons to receive presynaptic inputs from axons of other neurons, and they function to integrate and transfer information onto other neurons within a circuit. Recent studies have shown that axo-dendritic synapses may exhibit many different forms of plastic adaptation which can be categorised into two general groups. The first are known as Hebbian forms of plasticity, which include long-term potentiation (LTP) and long-term depression (LTD) (for reviews, see [2–4]). This form of plasticity is generally characterised as being input specific, whereby bursts of presynaptic activity, by causing postsynaptic depolarisation, can lead to a robust and persistent change in synaptic efficacy that can last for hours to months [5,6]. Additionally, this form of plasticity is identified as a positive feedback mechanism. For example, LTP induction renders a potentiated synapse to be activated with even greater ease than with stimuli before undergoing LTP, leading to the foreseeable problem that the extremities of neuronal activity can be reached unless a negative feedback mechanism is present to maintain overall dendritic activity. This regulatory process, belonging to the second group of plastic adaptation, is known as homeostatic plasticity, and it is used by neurons to stabilise synaptic strength and intrinsic excitability within an optimal operational range in order to modulate the efficacy of dendritic integration [7,8].

The properties of homeostatic processes are slowly being revealed. In particular, early studies in dissociated cell networks grown in culture have provided key insights. For example, using neocortical neurons, elevating network activity by acutely blocking $GABA_A$ receptors (with bicuculline) resulted in increased firing rates; yet upon sustained blockade (48 hours), the firing rate returned to basal levels [9•]. Alternatively, decreasing neuronal activity by expressing inwardly rectifying K^+ channel Kir2.1 to selectively hyperpolarise transfected hippocampal neurons, caused firing rates to decrease after 24 hours only to return to basal levels by 96 hours [10]. These findings suggest that neurons have developed sophisticated mechanisms to enable neuronal firing to be maintained within a set range despite the activity perturbations.

Additionally, network manipulations were shown to bi-directionally modulate synaptic strength. Miniature excitatory postsynaptic current (mEPSC) recordings showed an increase in amplitude after suppressing network activity but a decrease after increasing network activity [9•]. This phenomenon was termed synaptic scaling. This finding indicated that neurons could 'sense' network activity and undergo relevant synaptic changes (e.g. glutamatergic receptor accumulation) to homeostatically adapt their synaptic strength. Most of the previous studies whereby entire neuronal networks were manipulated with pharmacological agents suggested that homeostatic processes encompassed global changes causing synaptic strength to be scaled uniformly at all the synapses of the cell. However, recent reports suggest that homeostatic regulation of dendrites can occur through more local mechanisms [11,12•,13•,14,15].

Evidence for dendritic signalling in homeostatic processes

Research into the mechanisms underlying homeostatic processes using novel means of manipulating dendritic activity, has identified some interesting properties of homeostatic responses, pointing to multiple forms of adaptation.

It has been shown that postsynaptic depolarisation alone can induce homeostatic changes. Depolarising cells by elevating extracellular K^+ concentration in the presence of ionotropic glutamate and $GABA_A$ receptor inhibitors induced a decrease in quantal size [16]. This suggested that alterations in dendritic membrane potentials could be sufficient to trigger homeostatic quantal changes.

Subsequently, two studies examined the changes in dendritic activity using local microperfusion of pharmacological agents to address the nature of dendritic signalling involved in quantal scaling. First, Sutton *et al.* [13•] showed that neurons receiving a local inhibition of NMDA receptors in addition to a global TTX treatment, underwent a homeostatic increase in surface GluA1-containing AMPA receptors. This increase in GluA1-surface expression was constrained to the region of local perfusion of the NMDA receptor antagonist, was rapid (approx. one hour), and interestingly, it was dependent on local protein synthesis in dendrites. Second, Ibata *et al.* [17•] showed differential effects of local activity block at the soma or dendritic regions on surface GluA2 receptor expression. TTX perfusion onto the soma increased dendritic GluA2 levels but not when TTX was applied to the dendrites. These studies suggest that different homeostatic mechanisms may differentially regulate AMPA receptor subunits and that these mechanisms may operate within distinct neuronal subcompartments.

A novel approach to investigate whether homeostatic changes can be restricted to dendritic regions was taken by Ju *et al.* [15]. By physically isolating the dendrite from the soma of dissociated hippocampal neurons, they showed that GluA1 can be locally synthesised in dendrites in response to activity blockade by TTX and an NMDA receptor antagonist, and this event occurred independently of somatic activity, as corroborated later by Sutton and colleagues [13•]. Together, these studies show that certain forms of homeostatic adaptation can be locally regulated at the level of the dendritic subcompartment.

Rabinowitch and Segev [11,18] extend these observations to suggest that synaptic strength at individual synapses is regulated locally within dendritic subregions. A potential dilemma is posed by local homeostatic mechanisms when they co-exist at the same synapses undergoing Hebbian forms of plasticity. By acting to maintain dendritic activity within a set range, homeostatic processes could 'cancel out' Hebbian forms of synapse strengthening. Their theoretical study provides a potential solution, which proposes that the synaptic strength of neighbouring synapses decreases when a single synapse undergoes Hebbian potentiation [11,18]. In this situation, dendritic activity can be stabilised by homeostatic processes which scale the neighbouring synapses in the opposite direction to the synapses that have undergone Hebbian plasticity. This model suggests that the strength of single synapses along a dendrite can be altered independently to maintain dendritic activity within a set range whilst enabling Hebbian and homeostatic plasticity to co-exist.

A recent study in dissociated hippocampal cultures provides evidence that local dendritic activity can homeostatically regulate presynaptic release probability (p_r), a determining factor of synaptic efficacy. With the aid of styryl dyes and paired recordings to identify functional synapses between connected cell pairs, synapses along a given dendritic branch were shown to have p_r and the recycling pool size with a greater degree of similarity to each other than to synapses originating from the same axon formed onto other dendritic branches of the same postsynaptic cell [12•]. This indicated that there was some degree of dendritic compartmentalisation to the control of release probability. Intriguingly, p_r was shown to be negatively correlated with synapse number, suggesting that p_r could be scaled to a 'basal level' by distributing synaptic weight according to the number of synapses made onto a dendritic subregion. Focal dendritic stimulation also reduced p_r in targeted synapses in a manner dependent on dendritic activation, in further support of the hypothesis that spatially localised postsynaptic depolarisation may homeostatically regulate presynaptic release probability [12•].

Other reports are in agreement with the concept that postsynaptic mechanisms may homeostatically regulate presynaptic activity. Postsynaptic expression of Kir2.1 (and inducing hyperpolarisation) enhanced neurotransmitter release at the Drosophilia NMJ [19] and in dissociated cortical neurons (provided Kir2.1 was expressed after synapse formation) [10]. Another study using chronic network blockade of glutamate receptors also produced an increase in presynaptic release by promoting the rate of synaptic vesicle recycling [20].

These current studies indicate that homeostatic plasticity is not necessarily global, and local adaptation(s) can exist. Moreover, homeostatic processes can be expressed at the level of individual dendritic subregions with changes occurring at both the presynaptic and the postsynaptic sides. Further studies will be required to determine if and how different types of homeostasis encompass global and locally regulated changes in synaptic strength and whether they share common signalling components and pathways.

Dendritic Ca^{2+} signalling in homeostatic regulation

A role for dendritic depolarisation in homeostatic regulation as supported by a number of studies points to Ca^{2+} as a strong candidate for mediating at least some of the signalling in homeostatic mechanisms. Depolarisation of postsynaptic membranes can lead to Ca^{2+} entry into the cell through NMDA receptors, GluA2-lacking AMPA

receptors and voltage-gated Ca^{2+} channels, to activate a variety of intracellular signalling pathways and also trigger Ca^{2+} release from internal stores.

Ca^{2+} dynamics in dendrites has been widely studied [2,21]. Postsynaptic Ca^{2+} can diffuse a limited distance along the dendrite and potentially activate Ca^{2+}-dependent processes in nearby synapses [22,23]. The property of Ca^{2+} diffusion from dendritic spines to the shaft (or from shaft to spine in the case of Ca^{2+} increases resulting from backpropagating action potentials or dendritic spikes) is influenced by spine morphology including parameters such as the spine neck diameter and the spine length [24,25]; the diameter of the dendritic shaft offers another variable of Ca^{2+} dynamics [26]. The number and location of dendritic spines can also affect subcompartmentalisation of Ca^{2+} dynamics within the dendritic tree. An extensive study in hippocampal CA1 neurons has shown that spine density is highly heterogeneous where proximal dendrites within stratum radiatum have very low spine density in converse to distal dendrites, which are heavily populated with spines and receive a much larger proportion of Schaffer collateral inputs than proximal regions [27]. Therefore, synaptic integration may also be dendritically segregated and may influence the patterns of dendritic Ca^{2+} influx and diffusion. Moreover, the arborisation pattern of the dendritic tree and the number of Na^{+} channels have also been indirectly linked with the Ca^{2+} dynamics. For example, Ca^{2+} diffusion in cortical layer 2/3 pyramidal neurons was mainly restricted to proximal dendrites. This was correlated with the smaller amplitude and slower kinetics of dendritic Na^{+} action potentials with increasing distance from the soma, which suggested a relationship between dendritic depolarisation induced by somatic spiking and dendritic Ca^{2+} dynamics [28]. In addition to morphological properties, spatial and temporal control of intracellular Ca^{2+} is further provided by the endogenous Ca^{2+} binding proteins (e.g. calbindin D-28k, calretinin and parvalbumin [29]).

The extent of dendritic Ca^{2+} diffusion can be assessed with Ca^{2+} indicator dyes. Studies using such Ca^{2+} dyes have shown that Ca^{2+} signalling is usually transient (tens of ms) and limited by the uptake of Ca^{2+} into intracellular stores via sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump or removal to the extracellular space by plasma membrane Ca^{2+} ATPase [30,31]. Notably, despite such acute alterations in Ca^{2+} dynamics, some Ca^{2+}-dependent processes can manifest over many hours (see below). Together, Ca^{2+} signalling has appropriate spatial and temporal characteristics which may make it a suitable integrator of dendritic activity and membrane depolarisation for regulating the onset of homeostatic adaptation at individual synapses. Furthermore, Ca^{2+}-dependent changes in intrinsic excitability (see below) could also influence synaptic homeostasis.

The role of Ca^{2+} in inducing NMDA-dependent forms of LTP is well established. Ca^{2+} influx through NMDA receptors, as induced by high frequency stimulation of presynaptic inputs or glutamate application, can lead to the activation and translocation of Ca^{2+}/calmodulin-dependent kinase II (CaMKII) to synapses [32,33]. Activated CaMKII can then phosphorylate intracellular GluA1 and trigger the delivery of AMPA receptors to the cell surface [34,35]. It is currently unknown if a similar CaMKII-dependent phosphorylation of GluA1 occurs during homeostatic synaptic scaling. A recent timelapse imaging study demonstrated that spatially restricted activation of NMDA receptors by local application of glutamate and glycine to a small number of synapses, induced active CaMKII translocation to synapses within the application site. Intriguingly, the synaptic accumulation of αCaMKII and βCaMKII that was initially restricted spatially, was subsequently observed more widely at other synapses over the dendritic tree. This effect required postsynaptic Ca^{2+} influx and L-type Ca^{2+} channel activation and provided evidence that local membrane depolarisation may be propagated to yield more global synaptic effects involving Ca^{2+} signalling and CaMKII [36]. Other studies have indicated that CaMKII may retrogradely regulate presynaptic organisation and activity. Postsynaptic expression of constitutively active form of αCaMKII decreased presynaptic puncta density [37]. Moreover, postsynaptic transfection of αCaMKII or βCaMKII influenced quantal responses in opposite directions with αCaMKII transfected cells displaying a decreased frequency and slower decay rate of mEPSC and βCaMKII transfected cells showing an increased frequency and faster decay of mEPSC compared to controls [38]. Therefore, CaMKII signalling alone shows a capacity for intricate regulation of homeostatic synaptic plasticity. Whether the activation of other Ca^{2+}-dependent kinase cascades occur during homeostatic scaling of AMPA receptors and presynaptic changes remains to be determined.

Ca^{2+} and homeostatic control of intrinsic excitability

The intrinsic excitability of neurons can be altered in response to changes in neuronal activity. This adds another layer of complexity in homeostatic synaptic regulation because intrinsic excitability, in turn, could influence activity-dependent synaptic plasticity. Computational modelling studies demonstrated that the levels of intracellular Ca^{2+} were correlated to neuronal firing rate, and the changes in Ca^{2+} levels could modify neuronal excitability by changing voltage-gated channel conductances, possibly by altering the channel number [39]. Experimental support was provided by a study in neurons of lobster stomatogastric ganglion, where Ca^{2+} was necessary for the homeostatic regulation of voltage-gated channel density that was required for depolarisation associated burst firing [40,41]. In this study, depolarising dissociated neurons produced

changes in the size and kinetics of intrinsic currents over time. Firstly, a fast inactivation current was observed after day 1, followed by tonic firing of action potentials after day 2 and finally oscillatory bursting activity was observed after days 3–4. Experimental and modelling data suggested that these intrinsic changes in firing rate were a result of changes to the balance of inward and outward current densities and ionic conductance [41].

An extension of this finding was made in dissociated visual cortical neurons where the balance of Na^+ and K^+ conductances affected the intrinsic excitability and firing rate of a neuron. Chronically suppressing network activity with TTX saw a gradual increase in the firing frequency over time. Moreover this manipulation differentially altered channel conductance with an increase in the amplitude of Na^+ currents and a decrease in persistent K^+ currents but with no alterations in Ca^{2+} or transient K^+ currents. Therefore, specific channels could be upregulated or downregulated in response to activity to modulate firing rates of the cell [42•]. Liu and Kaczmarek showed that intrinsic excitability could also be decreased by Ca^{2+}-dependent processes, involving Ca^{2+} influx following depolarisation and elevated K^+ channel transcription and current density [43]. Neurons thus can make use of transcriptional control to regulate channel abundance to modify excitability in response to changes in network activity. Future studies examining the subcellular localisation of newly delivered channels may provide insights into whether excitability is altered on a local or global scale. Nevertheless, even if receptor density or conductances are adjusted locally in dendritic subregions, global effects on the function of the cell may still be exhibited. For example, in neocortical layer 5 neurons, a local decrease in voltage-gated Na^+ channels in the proximal dendrites may affect action potential backpropagation to distal dendrites and influence forms of plasticity that are dependent on dendritic action potentials [44,45].

Ca^{2+} signalling and synaptic scaling

A recent study by Ibata *et al.* [17•] demonstrated that synaptic scaling required Ca^{2+}-mediated transcriptional processes. TTX treatment for four hours increased cell surface GluA2 fluorescence and mEPSC amplitude, and local cell body application of TTX to block somatic Ca^{2+} transients, as verified by applying a broad spectrum Ca^{2+} channel blocker $NiCl_2$, was sufficient to induce synaptic scaling. Intriguingly, like the TTX treatment, $NiCl_2$ alone also generated an increase in GluA2 fluorescence suggesting that inhibiting somatic Ca^{2+} spiking and suppressing Ca^{2+} influx alone could lead to homeostatic changes. The authors propose that the decrease in somatic Ca^{2+} also decreases signalling of the transcriptional regulator CaMKIV, and the observed block of TTX-induced scaling up of synaptic GluA2 by the application of transcriptional inhibitors suggests that transcriptional processes regulated by CaMKIV mediate homeostatic synaptic scaling.

Reports investigating the class of Ca^{2+} channels involved in homeostatic scaling have resulted in some differences. In one study in cortical neurons, the scaling down of mEPSC amplitude with postsynaptic depolarisation could not be blocked by nifedipine (L-type Ca^{2+} channel blocker), suggesting that this effect was independent of Ca^{2+} influx through L-type Ca^{2+} channels [16]. However, in hippocampal neurons, bath application of nifedipine was sufficient to scale up GluA2-lacking synaptic AMPA receptors [46], and in cortical neurons, somatic perfusion of nifedipine-induced GluA2-containing AMPA receptor accumulation was similar to that seen with TTX treatment (see above) [17•]. This latter effect was not observed with ω-conotoxins (to block P/Q and N channels), indicating that homeostatic changes to activity suppression were at least in part mediated by the suppression of Ca^{2+} influx through L-type Ca^{2+} channels. One possible explanation for this difference is that different Ca^{2+} channels are required for activity elevation and others for activity suppression by coupling to distinct signalling pathways.

Future studies examining the role of Ca^{2+} in homeostatic plasticity may reveal greater insights into the potential Ca^{2+}-dependent intracellular signalling pathways involved and if there are any spatial rules to Ca^{2+} regulation of homeostatic processes.

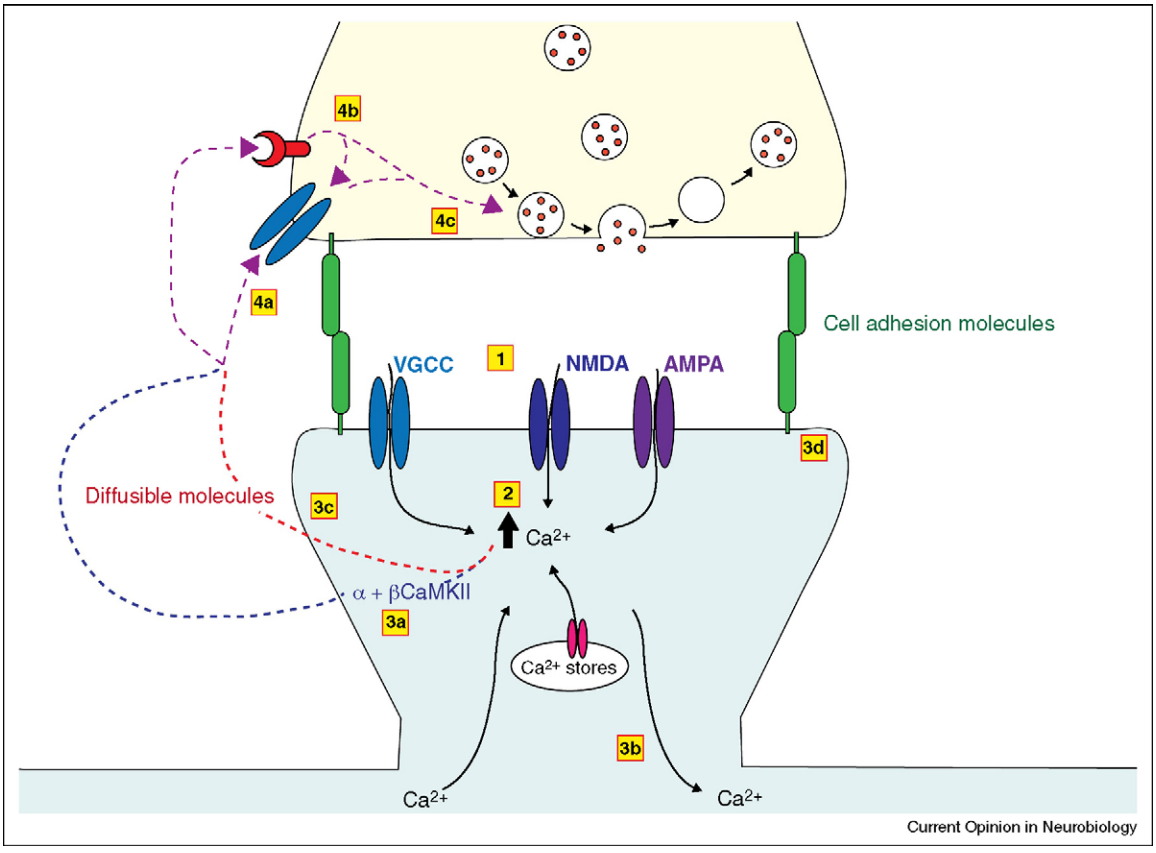
Potential mechanisms for postsynaptic modulation of presynaptic activity

The molecular mechanisms by which the levels of dendritic depolarisation and Ca^{2+} modulate synaptic strength parameters are areas of active current research. In particular, mechanisms of activity-dependent control of postsynaptic receptor composition and abundance have received considerable attention over the recent years (reviewed in [7,47]; also see [48,49]). Here we will focus on the less well-understood regulation of presynaptic neurotransmitter release by the levels of dendritic activity. One possible mechanism involves retrograde messengers. These are often diffusible small molecules which pass from the postsynaptic spine, across the cleft to act on presynaptic terminals. Another mechanism could involve *trans*-synaptic proteins, which by bridging the synaptic cleft through heterophilic or homophilic interactions can directly modulate the structure and function of both the presynaptic and the postsynaptic terminals. These and other examples of potential signalling components are discussed below (see Figure 1).

Diffusible molecules

Diffusible messengers that have been previously implicated in activity-dependent presynaptic changes are

Figure 1



Potential players of homeostatic feedback modulation of presynaptic neurotransmitter release by postsynaptic activity. Depolarisation of postsynaptic membranes enables Ca^{2+} influx into spines through voltage-gated Ca^{2+} channels (VGCC), NMDA receptors and GluA2-lacking AMPA receptors (1). The increase in intracellular Ca^{2+} (2) may also arise from activity-dependent triggering of IP_3 and ryanodine receptors causing Ca^{2+} release from internal stores. This elevation of cytoplasmic Ca^{2+} can act on a range of signalling pathways locally within the spine, for example, by activating postsynaptic Ca^{2+}-dependent kinases including αCaMKII and βCaMKII (3a), to produce changes in presynaptic function. In addition, Ca^{2+} can induce widespread action by diffusing into the dendritic shaft (3b). Postsynaptic Ca^{2+} signalling may also lead to the production of diffusible molecules such as endocannabinoids and BDNF, which retrogradely act on the presynaptic terminal (3c). Other diffusible molecules including nitric oxide, arachidonic acid, adenosine and platelet activating factor have also been shown to act as retrograde messengers. Cell adhesion molecules can also modulate presynaptic activity through *trans*-synaptic signalling mechanisms (3d): these include neuroligin–neurexin complex, N-cadherins, integrins, NCAMs and Eph/ephrins. Activation of postsynaptic signalling pathways, release of diffusible molecules and action of cell adhesion molecules can influence neurotransmitter release by altering Ca^{2+}-influx through presynaptic VGCC either directly (4a) or indirectly through the activation of presynaptic signalling pathways (4b) and by altering the synaptic vesicle cycle (4c). Although not illustrated here, presynaptic terminal density can also be influenced by postsynaptic feedback processes.

plausible candidates also for homeostatically adjusting the presynaptic release properties according to the level of dendritic activity. In particular, endocannabinoids have been shown to function as retrograde messengers at CNS synapses. The endocannabinoids are arachidonic acid derivatives found in many regions of the CNS with particularly high concentrations in the hippocampus, striatum and brainstem [50]. In response to a range of stimulation protocols the postsynaptic neuron can generate endocannabinoids that diffuse across the synaptic cleft and activate CB1 receptors on the presynaptic bouton, which, by altering the presynaptic Ca^{2+} influx, reversibly modifies presynaptic release probability [51–53].

Recent studies have shown that postsynaptic depolarisation can lead to endocannabinoid production at both glutamatergic synapses (depolarisation-induced suppression of excitation (DSE)) [54,55] and GABAergic synapses (depolarisation-induced suppression of inhibition (DSI)) [56,57]. Furthermore, postsynaptic Ca^{2+} influx was necessary and sufficient for these two forms of short-term plasticity as postsynaptic uncaging of Ca^{2+} stimulated DSI [53] whereas postsynaptic Ca^{2+} chelators blocked DSI and DSE [54,57]. The role of Ca^{2+} in endocannabinoid synthesis and release is not fully understood but it has been proposed to activate Ca^{2+} sensitive enzymes such as PLD and PLCβ implicated in endocannabinoid production [58,59].

Endocannabinoids have also been implicated in many long-term plasticity studies (for extensive review see Chevaleyre *et al.* [51]) suggesting that postsynaptic production and the release of endocannabinoids can be triggered by many different stimulation paradigms. Interestingly, a form of endocannabinoid-mediated amygdalar heterosynaptic LTD [60] was triggered using a low-frequency stimulation (1 Hz) not too dissimilar to the frequencies (2 Hz) adopted by Branco *et al.* [12•] where homeostatic downregulation in p_r in response to local dendritic stimulation was observed in hippocampal neurons. Thus, whilst highly speculative, parallels may exist in the molecular mechanisms underlying certain forms of LTD and homeostatic reduction in synaptic strength, possibly involving the endocannabinoids.

In summary, the broad expression of endocannabinoids, the ease with which they can be released in response to postsynaptic activation, including the broad range of stimulus, and the direction of its effect, namely, suppression of neurotransmitter release upon increased postsynaptic activity, are attractive properties for homeostatic downregulation of presynaptic strength. Future research will determine if this and other retrograde messengers that have been implicated in Hebbian plasticity (e.g. nitric oxide, arachidonic acid, adenosine and platelet activating factor) will play roles in homeostatic processes [52,61]. Notably, the neurotrophin BDNF whose role in Hebbian plasticity is well established, has also been shown to play a role in homeostatic synaptic plasticity [7]. In addition, there may be diffusible factors that are unique to regulating homeostatic synaptic plasticity. For example, TNFα released from glial cells is dispensable for LTP or LTD but is required for TTX-induced synaptic scaling [62]. Whether TNFα plays a role in the setting of presynaptic strength during homeostatic plasticity remains to be addressed.

Cell adhesion proteins

Another class of potential candidates for mediating *trans*-synaptic homeostatic regulation are cell adhesion proteins. In addition to their structural role in organising the synaptic junction, a number of cell adhesion molecules have been proposed as potential regulators of synaptic plasticity through *trans*-synaptic signalling. Moreover, adhesion via the extracellular matrix could also contribute to homeostatic control of synaptic strength. Here we describe examples for their putative roles in coupling postsynaptic activity with the homeostatic regulation of presynaptic release.

A recent study has implicated the N-cadherin/β-catenin complex in modulating synaptic scaling. Eliminating postsynaptic β-catenin, a condition that compromised the adhesive strength of homophilic N-cadherin interactions, prevented bi-directional scaling of quantal size induced by a global pharmacological inhibition or enhancement of network activity [63], whilst producing changes in presynaptic architecture [64]. Moreover, a lack of postsynaptic N-cadherin exacerbated pulse train depression, consistent with a reduction in presynaptic release probability [65]. Collectively, these findings suggest a possible contribution of *trans*-synaptic signalling by the N-cadherin/β-catenin complex in regulating homeostatic regulation of presynaptic and postsynaptic strength.

Recently, postsynaptic β3 integrins have been shown to be required for synaptic scaling of GluA2 receptors. Chronically suppressing network activity with TTX increased surface GluA2 receptor and β3 integrin levels, whilst elevating network activity with bicuculline decreased surface GluA2 and β3 integrin levels. Additionally, synaptic scaling could not be induced in dissociated and slice cultures from β3 integrin knockout mice [66]. Interestingly, the increase in surface β3 integrin and GluA2 levels observed during TTX treatment was mimicked by exogenous application of TNFα, suggesting that β3 integrin signalling during synaptic scaling may act in concert with TNFα released from glial cells [62,66]. A possible role for β3 integrins in modulating presynaptic activity at developing synapses has been proposed [67], although it is not clear if β3 integrins directly regulate p_r at mature synapses. Notably, at mature synapses, integrin inhibitors produced a transient increase in mEPSC frequency, implicating a presynaptic role for integrin signalling [66]. It would be of interest to further investigate whether and how integrins, of which there are many subunits [68], control presynaptic homeostatic plasticity.

Another potential candidate is the heterophilic coupling of postsynaptic neuroligin and presynaptic β-neurexins [69], whose role in *trans*-synaptic signalling at developing synapses has been elegantly shown using co-culture of pontine nucleus explant and cerebellular granule cells [70]. Postsynaptic expression of neuroligin induced presynaptic differentiation and clustering of functional synaptic vesicles in pontine axons, suggesting a specific *trans*-synaptic role for neuroligin [70]. A recent electrophysiological study went one step further to show that such activity for neuroligin and neurexin was not limited to developing synapses. Neuroligin complexed to postsynaptic scaffold protein PSD-95 modulated paired-pulse ratio of evoked synaptic responses, a measure of presynaptic release probability, in a *trans*-synaptic fashion at functional synapses [71]. This raises the possibility that neuroligin–neurexin interaction could implement the *trans*-synaptic coordination of activity-dependent synaptic plasticity (see [72]). It would be of interest to further examine a role for these and other classes of cell adhesion proteins (e.g. Eph/ephrins and NCAMs [73,74]) in the homeostatic regulation of presynaptic strength to changes in postsynaptic activity.

Conclusions

Research into the molecular and cellular mechanisms underlying homeostatic plasticity has flourished in recent years. Here we have focused on dendritic signalling and highlighted several studies which have put forward the idea that homeostatic adaptation can be regulated in dendrites in response to global and local activity manipulations. We then considered Ca^{2+} and a number of retrograde signals for their potential roles in exerting homeostatic control over the neuronal network activity by modifying intrinsic activity and synaptic strength. The complexity of regulatory processes underlying homeostasis is underscored by the reports of different forms of adaptations depending on factors such as the timing and duration of activity interference, developmental maturity of neurons and the neuronal types to list a few. In addition, although not discussed here, a key area of study in homeostatic synaptic scaling is activity-dependent mechanisms of postsynaptic receptor trafficking (reviewed in [7,47]; also see [48,49]). The abundance and composition of postsynaptic receptors are intricately controlled by neuronal activity, involving multiple scaffolding interactions and a myriad of signal transduction cascades.

In spite of the recent advances in delineating the mechanisms of homeostatic plasticity, many questions remain. How many different forms of homeostatic plasticity exist, and what are the precise molecular players and signalling pathways for each? Beyond cell type differences, are there differences in regions of the dendritic arbour, for instance, are basal dendrites regulated in the same way as apical dendrites and are there any variations in the regulatory processes of distal and proximal dendrites? To what extent are local changes in dendritic activity confined to local synaptic changes or can they influence the function of the whole cell, and if so, how do the signals spread across the entire neuron? Another interesting aspect of homeostatic plasticity is to better understand the dynamic interaction between excitatory and inhibitory inputs during homeostatic adaptation, as most of the studies to date have focused on either excitatory or inhibitory synapses individually. Altogether, further studies *in vivo* where the native dendritic architecture and the organisation of synaptic inputs are preserved, are warranted for a detailed cellular and physiological understanding of homeostatic regulation. Complementing such studies, investigations from culture systems that are highly amenable to molecular approaches and manipulation of single synapses, would help provide novel insights into the molecular mechanisms involved in the dendritic signalling of different types of homeostatic processes.

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