# Synaptic gain control and homeostasis

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Chronic changes in activity can induce neurons to alter the strength of all their synapses in unison. Although the specific changes that occur appear to vary depending on the experimental preparation, their net effect is to counter the experimentally induced modification of activity. Such adaptive, cell-wide changes in synaptic strength serve to stabilize neuronal activity and are collectively referred to as homeostatic synaptic plasticity. Recent studies have shed light on what triggers homeostatic synaptic plasticity, whether or not it is distinct from other forms of synaptic plasticity and whether or not it occurs in the intact brain.

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**Abbreviations**

| | |
|---|---|
| **BDNF** | brain-derived neurotrophic factor |
| **CaMK** | calcium/calmodulin-dependent protein kinase |
| **mEPSC** | miniature excitatory postsynaptic current |
| **NMDA** | N-methyl D-aspartate |

## Introduction

Neural circuits and their elements adapt to changes in their environment. Over short time scales, adaptation serves to increase information transfer by neurons [1]. For example, if the response of a sensory neuron consistently falls outside of its dynamic range, the gain (the magnitude of the neuronal response for a given stimulus) is adjusted to bring the response back to the appropriate dynamic range [1]. For central neurons whose inputs arrive through synapses with other neurons, a major component of this adaptation occurs at the synapses themselves. Depending on the time scale of these changes, different terms such as plasticity, potentiation, augmentation or depression are used [2]. In effect, however, they all serve to control the gain of the synapse.

Short-term synaptic adaptation — over a time scale of milliseconds to seconds — has been related to neuronal function in a few cases [3–5], and is largely mediated by presynaptic changes [2]. Longer-term changes in synaptic strength also occur over a time scale of hours to days. Historically, much attention has been paid to Hebbian plasticity, in which presynaptic and postsynaptic activities locally interact at individual synapses to induce lasting changes in strength [6,7]. Hebbian plasticity, under some conditions, risks runaway strengthening or weakening of synapses, which leads to a saturation of synaptic strength [8]. In effect, this erodes the dynamic range of a neuron, and is akin to setting the gain of a sensory neuron too low or too high. To avoid saturation, neurons are thought to have a way of re-establishing normal synaptic strengths while maintaining the relative strengths of all synapses. Such global renormalization of synaptic gain has been described in terms of homeostatic synaptic plasticity and has gained experimental support [9–11]. Below, we discuss the exact meaning of homeostatic plasticity, and review some of the recent experimental findings. For the sake of brevity and clarity, we confine ourselves mainly to mammalian systems. We also focus on synaptic homeostasis, leaving out other forms of neuronal compensation [9].

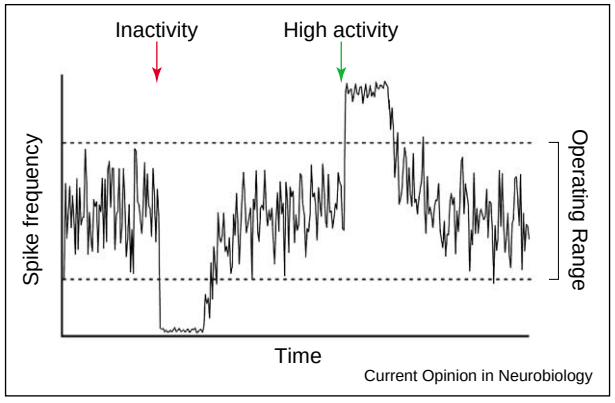
## Homeostasis and synaptic adaptation

The concept of homeostasis arose in physiology some 70 years ago, the term first being coined by Cannon in 1932 [12]. Certain physiological parameters, core temperature and blood pressure for example, must be maintained within a narrow range — in fact, a range so narrow that it becomes a set point — for the survival of an organism. Environmental (or internal) changes that push the biological system away from its equilibrium also trigger compensatory changes that return the system to its set point. Thus, paradoxically, a stable biological system remains constant by being able to change and evolve.

As mentioned earlier, the term homeostasis has recently been brought to the realm of synaptic physiology [13,14]. When the activity of neurons (or muscle fibers in the case of the neuromuscular junction) is pushed beyond the normal operating range, a form of adaptation occurs that changes the gain of all synapses equally. The important consequence of such a mechanism of synaptic gain control is that neurons can stabilize their excitability while retaining relative differences in strength among synapses.

The return to a homeostatic set point upon perturbation makes immediate sense to structures that are expected to have a reproducible and reliable pattern of activity — for example, the activity of muscle fibers [11]. In other systems, however, it is not immediately clear how homeostasis can be useful when diversity in neuronal activity is

**Figure 1**




Maintaining neural activity within a range. Neuronal activity (for example, the rate of action potentials) is normally maintained within an operating range, rather than at a fixed set point. When firing frequency either falls below (red arrow) or rises above (green arrow) the operating range, homeostatic plasticity brings it back to its optimal limits. The time course of return is not exactly known, but is thought to be several hours.

required. If every neuron is forced to return to a fixed firing rate every time it strays from a set point, then all neurons will have similar levels of activity and diversity would be abolished. There are several ways to deflect this concern. First, one can dispense with the idea of a fixed set point, replacing it with a range of activity (Figure 1). In this case, homeostatic plasticity would act as a safety barrier to ensure that neurons do not reach extremes of activity — epilepsy or complete silence. Second, each cell can have its own individual set point, allowing a diversity of average activity among neurons. At present, there is little information on the variability in average firing rates (averaged over long times) within a population of neurons of a particular class under physiological conditions.

## Global or local rules?

A crucial question regarding homeostatic plasticity is whether or not such regulation of synaptic gain requires an explicit global or cell-wide renormalizing mechanism. Alternatively, local rules for synaptic change might be sufficient to account for homeostatic regulation. For example, the Bienenstock-Cooper-Munro sliding threshold model for synaptic plasticity can predict stability of neuronal activity in the face of Hebbian modification of synapses [15,16]. In this model, as synapses get stronger it becomes progressively more difficult to strengthen them further, and easier to depress them. The threshold for potentiation is usually set globally for the entire neuron to preserve the relative strengths of individual synapses.

Synaptic learning rules that introduce competition among synapses can also produce stable networks without the need for a global normalizing variable [8,16]. For example, experiments suggest that strengthening a particular set of synapses can lead to heterosynaptic depression of other synapses [17,18]. In an elegant variant of this idea, it has been proposed that the modern version of Hebb's rule, referred to as 'spike-timing-dependent plasticity', can automatically give rise to competition among synapses [16,19]. Here, synaptic modification is driven by precise timing relationships between pre- and postsynaptic spikes. The window of coincidence within which pre- and postsynaptic action potentials must occur is smaller for strengthening than for weakening. This asymmetry in the coincidence window leads to competition among different input synapses of a neuron, and curtails unbounded growth or loss of synapses.

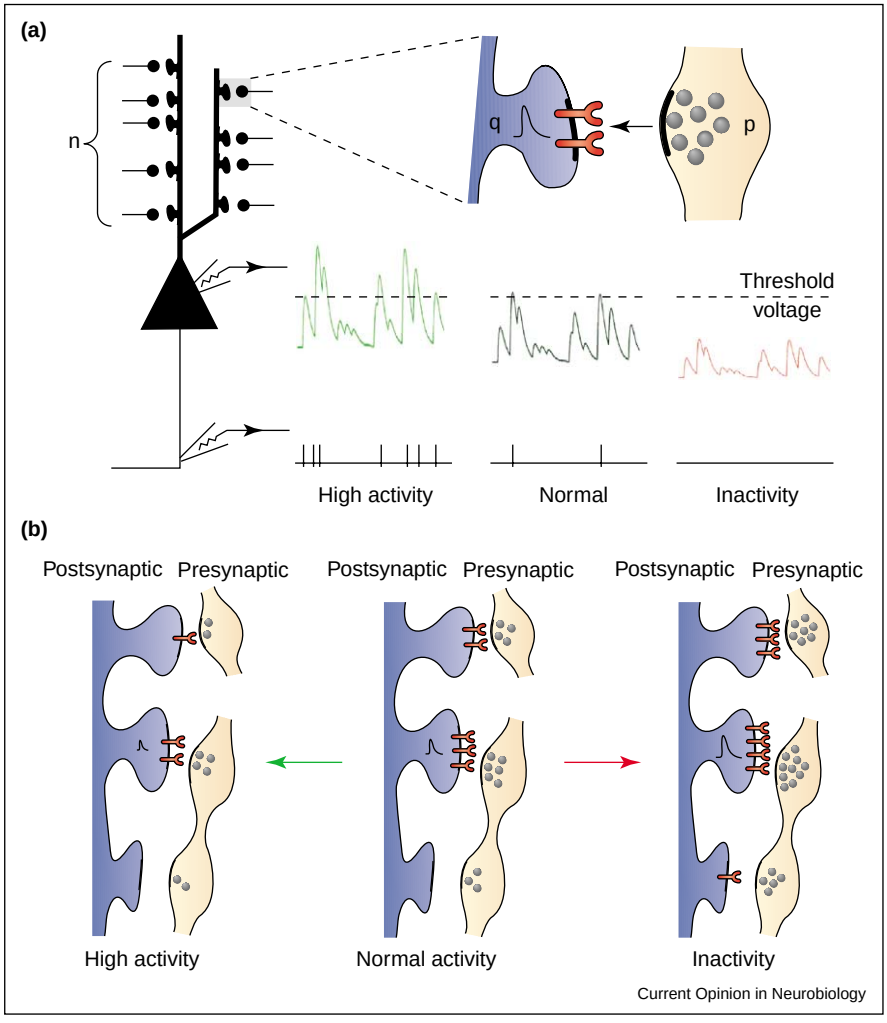
Even if local rules of synaptic modification could, in principle, account for homeostasis, experimental evidence from simple networks hints at the existence of other mechanisms that are different from the standard forms of synaptic plasticity. We discuss these experiments below.

## What is altered when you push the envelope?

Mechanistic studies of homeostatic plasticity have typically relied on pushing activity levels to extremes — either a complete block or very high activity levels [10,11]. These studies have found that there are different ways in which neurons adjust their synapses to adapt to these manipulations (Figure 2). In cortical cultures, chronic silencing of all neurons with tetrodotoxin (TTX) or with glutamate receptor antagonists results in a larger quantal amplitude, with little effect on the number of synapses or the frequency of miniature excitatory postsynaptic currents (mEPSCs) [14,20]. In this preparation, other manipulations of activity also alter quantal amplitude without changes in other parameters [14,21,22]. The changes in quantal amplitude appear to correlate well with changes in the number of glutamate receptors expressed on the cell's surface [23–26]. Similar effects have been observed in cultures of spinal cord neurons [27]. By contrast, suppressing activity in hippocampal neurons in culture causes only a modest increase in the quantal amplitude, but a large increase in the frequency of mEPSCs [28,29••,30•]. A similar phenotype is also seen in hippocampal organotypic slice cultures at different stages in development (W Tyler, L Pozzo-Miller, personal communication, [31,32]). Inhibition of N-methyl D-aspartate (NMDA) receptors in organotypic slice cultures for an extended period of two weeks leads to an increase in mEPSC frequency and the formation of new synaptic connections [33].

How can the apparently different results from cortical and hippocampal neurons be reconciled? One possibility is that in hippocampal neurons, silent synapses become unmasked after glutamate receptor insertion at postsynaptic sites [23]. This will have the effect of increasing mEPSC frequency, as more synapses become functional,

**Figure 2**




Homeostatic mechanisms are triggered by changes in activity levels. **(a)** In a simplified view, three general parameters determine the total excitatory synaptic input to a neuron: the number of synapses or release sites (n), the release probability of individual presynaptic terminals (p) and the quantal amplitude defined as the postsynaptic response to the contents of a single vesicle (q). Synaptic inputs are integrated in the somato–dendritic compartment of the neuron (black traces), and an action potential is triggered when a threshold voltage is reached (dashed line). If the inputs to a neuron are attenuated (for example by decreasing membrane resistance through the overexpression of a potassium channel) or if the membrane potential is hyperpolarized (red trace), the neuron would fire fewer action potentials. Conversely, amplification of synaptic inputs or depolarization of the membrane (green trace) will lead to an increase in the firing rate. To compensate for these changes in activity, neurons change the strength of their synapses by modulating one or more of the synaptic parameters shown in panel (b). **(b)** In hippocampal neurons, homeostatic plasticity appears to involve changes in both pre- and postsynaptic strength. During inactivity (red arrow), insertion of glutamate receptors into postsynaptic spines could result in an increase in quantal amplitude (q) and may also uncover silent synapses (n). On the presynaptic side, an increase in the number of neurotransmitter-filled vesicles occurs, which correlates with an increase in release probability (p). The opposite is expected when activity reaches extremely high levels (green arrow).

and at the same time increasing mEPSC amplitude modestly. Changes in presynaptic structure and function, however, clearly occur in inactive hippocampal neurons, which suggests a parallel increase in both pre- and postsynaptic strength [34•]. This is in agreement with a parallel increase in mEPSC frequency and quantal amplitude [29••,30•]. It is possible, of course, that intrinsic differences among neuronal types cause different reactions to similar manipulations.

Extreme changes in activity also appear to regulate NMDA receptor expression under some conditions. Chronic inactivity increases the number of synaptic NMDA receptor clusters in hippocampal cultures [35]. In cortical cultures, the amplitude of the NMDA receptor-mediated mEPSC increases with inactivity [20]. Similar increases have been observed in hippocampal neurons treated with TTX (J Burrone, VN Murthy, unpublished data). Surprisingly, immunocytochemical studies do not

find an increase in the number of NMDA receptors per synapse [23–26].

At the fly neuromuscular junction, manipulation of several proteins at the synapse causes a compensatory adaptation in synaptic structure and function [11,36]. Of particular interest is the recent experiment by Davis and co-workers who overexpressed an inwardly rectifying potassium channel, Kir2.1, in single muscle fibers and lowered its resting membrane potential and membrane resistance [37•]. Synaptic inputs should fail to elicit action potentials in the muscle, rendering it silent. Remarkably, nerve-evoked synaptic depolarization of the muscle was similar to wild type because of a homeostatic increase in presynaptic release probability, with no change in quantal amplitude. Changes in quantal amplitude, however, have been shown to occur in response to other manipulations [38].

Although we have focused on excitatory synapses, it is worth noting that inhibitory synapses also undergo homeostatic regulation. Activity suppression appears to reduce the amplitude of miniature inhibitory postsynaptic currents (mIPSC) in cortical cultures, with little change in the frequency of mIPSCs [39]. In general, whether the changes are presynaptic or postsynaptic, whether they are for inhibitory or excitatory synapses, they conspire to compensate for altered activity and promote stability.

## Mechanisms in homeostatic plasticity

What activity-related variable is sensed in synaptic homeostasis? Some obvious candidates are membrane depolarization, a measure of spike activity (mean rate or peak rate, for example), and average calcium influx. All of these variables are closely related and it may prove difficult to tease them apart.

At the *Drosophila* neuromuscular junction, homeostatic plasticity can be triggered by selectively hyperpolarizing individual muscle fibers, which suggests that altered membrane depolarization is sufficient to trigger compensatory changes [37•]. It must, however, be noted that the hyperpolarization was rather severe and resulted in the absence of muscle action potentials. A similar approach has also been recently used in dissociated hippocampal cultures, in which Kir2.1 was selectively overexpressed in an individual neuron at different stages in the development of the circuit [29••]. When a neuron was inhibited after synapse formation, an increase in synaptic input led to a recovery of the firing rate back to control levels. In cortical cultures, this issue was addressed by depolarizing all cells uniformly with different concentrations of potassium chloride [22]. As expected, synaptic gain scaled inversely with the degree of depolarization: the larger the depolarization, the lower the gain [10].

Although altered membrane depolarization can trigger homeostatic plasticity, neurons appear not to renormalize the membrane potential; rather, the variable that is restored is the spike frequency. Suppression of fast inhibitory synaptic transmission initially elevates firing rates of cortical neurons in culture. However, over several days, the average firing rate of these neurons returns to control levels [14,40], although the firing pattern is altered to high-frequency bursts [40]. Conversely, within 3 days of reducing firing frequency using Kir2.1 overexpression in individual neurons, the frequency returns to normal levels [29••]. Suppressing action potentials with tetrodotoxin also triggers homeostatic changes, which suggests that spikes or their downstream effects such as calcium entry are important [10]. Taken together, these results illustrate the importance of average spike frequency in homeostatic plasticity.

Variation in the concentration of intracellular calcium could also report changes in neuronal activity. Changes in intracellular concentration of calcium could, in principle, explain both the importance of membrane depolarization and spike frequency in homeostatic plasticity. Activity-dependent entry of $Ca^{2+}$ can occur through many different routes, including voltage sensitive $Ca^{2+}$ channels and NMDA receptors. To date, there is no conclusive evidence for either channel playing a role in homeostatic plasticity, and in at least one preparation neither channel appears to be required for homeostatic plasticity [22]. It is likely that multiple routes of calcium entry play redundant roles, complicating the analysis.

Calcium is also a particularly attractive variable in homeostatic plasticity, as many calcium sensors are involved in regulating synaptic strength. Indeed, recent work in dissociated hippocampal cultures suggests that the calcium/calmodulin-dependent kinase II (CaMKII) may be involved in homeostatic plasticity [30•]. The ratio of the level of expression of the two main isoforms of CaMKII, α and β, is tightly regulated by activity and correlates with changes in synaptic strength [30•]. Although it is natural to focus on calcium, it is important to remember that electrical activity also sets in motion other second messenger cascades. Intracellular concentration of cAMP, for example, rises in response to increased neuronal activity and in turn modulates protein kinase and phosphatase cascades, which eventually lead to control of gene expression [41].

What exactly do the signaling cascades activate, and how do they lead to changes in synaptic gain? A recent study has shown that the turnover rates of many postsynaptic proteins, including glutamate receptors, are altered by activity [42•]. Changes in protein turnover, which involves the ubiquitin-proteasome system, lead to changes in the steady state amount of proteins at the

synapse and may account for the postsynaptic changes in synaptic gain. In addition, gene expression levels are altered by activity, although it is not clear at present whether regulation of transcription or translation contributes to homeostatic synaptic plasticity. Although local translation may be important for some forms of synaptic plasticity, regulation of gene expression appears likely to occur in homeostasis as the changes involved are cell-wide. Chronic changes in activity lead to alterations in calcium/cAMP responsive element binding protein (CREB) and ERK/MAPK signaling, which suggests that changes in gene expression are involved [42•]. Understanding how gene expression is regulated in an activity dependent manner is likely to require uncovering how $Ca^{2+}$-sensitive transcription factors such as CREB modulate gene expression and ultimately synaptic function [41]. The targets of CREB and similar transcription factors are diverse and include the important neurotrophin, brain-derived neurotrophic factor (BDNF). Neurotrophins such as BDNF are likely to play a role in homeostatic synaptic plasticity [21,43].

The precise connection between gene expression and postsynaptic function is unclear, but probably involves intracellular pathways that regulate receptor traffic and the assembly of synaptic molecular complexes. Presynaptic changes resulting from postsynaptic sensing of activity require additional unknown steps, in particular, intercellular retrograde communication [44]. It is unclear what these retrograde messengers are, but they could be diffusible substances such as cannabinoids [45], or extracellular or membrane-spanning cell adhesion molecules, or even developmental morphogens, such as the Wnt proteins [46].

## Single neurons versus populations

Investigation of homeostatic plasticity has typically involved drastic alteration of activity in large populations of neurons [10]. What happens when activity is manipulated more selectively in a small number of neurons? To address this, the inwardly rectifying potassium channel Kir2.1 was used to reduce activity selectively in individual neurons in an otherwise normal network [29••]. In line with previous expectations, homeostatic plasticity was observed when suppression began after synapses were established. In contrast to this outcome, when activity was suppressed in younger neurons with few synapses, the number of synaptic inputs was reduced — an effect opposite to homeostasis [29••]. Importantly, this reduction did not occur when activity in all neurons was suppressed, suggesting that differences in activity levels are important for the non-homeostatic response. Why younger neurons do not undergo homeostatic plasticity when activity is selectively suppressed is unclear. Differences in gene expression between younger and older neurons might contribute to the differences in responses to activity suppression.

The difference in manipulating activity between all neurons and individual neurons is also highlighted by studies in mixed cultures of wild type neurons and neurons from knockout animals. For example, when co-cultured, neurons lacking the neural cell adhesion molecule receive fewer synapses than nearby wild type neurons [47]. This asymmetry was abolished when excitatory synapses were blocked chronically in cultures. A bias in synapse number was also seen in mixed cultures of synaptophysin-null neurons and wild type neurons; the bias was again abolished when activity was blocked [48]. These examples indicate that whether homeostatic synaptic plasticity is triggered or not depends on the exact nature of the activity manipulation.

## Homeostatic synaptic plasticity in the brain

Is there evidence for homeostatic regulation of synapses in the brain? Activity appears to have little or no effect on the initial formation of synapses in most regions of the brain [49]. Although dispensable for the initial formation of synapses, activity is necessary for sculpting precise circuits by means of selective synapse elimination and consolidation.

In many regions of the brain, the number of release sites terminating on a given postsynaptic neuron increases during development, even if the number of axons innervating the neuron might decrease [50]. Consequently, the total excitation to a neuron would increase should synapses maintain their initial strength. This is countered, in part, by the increasing complexity of the dendritic arbor and decreasing input impedance, which reduce the excitability. In some cases, a reduction in the quantal amplitude might represent an additional way of compensating for the increase in the number of release sites. A recent study in the rat visual cortex showed that during a period of marked synaptogenesis (postnatal day 12 to 18), there is an increase in mEPSC frequency accompanied by a decrease in mEPSC amplitude in layer 4 neurons [51••]. This reduction in quantal amplitude was substantially delayed by sensory deprivation, by either dark rearing or monocular injection of tetrodotoxin [51••]. The authors suggest that homeostatic mechanisms might normally contribute to the attenuation of quantal amplitude, but they fail to occur in the absence of sensory-evoked activity.

Caution is needed before generalizing these results, as intracellular recordings from neurons in many cortical regions *in vivo* do not support conservation of excitation — in fact, the firing rates [52,53] and the total synaptic input increase dramatically during development [54]. Furthermore, an inverse relation between mEPSC frequency and amplitude is not observed in all regions of the brain. In the hippocampus, a region of the brain with similar neuronal types to the cortex, an increase in mEPSC frequency is not accompanied by a significant

decrease in quantal amplitude [55]. Interestingly, inhibitory synapses in the hippocampus do show such an inverse relation [56]. In neurons that receive input from only a few fibers, for example the retinogeniculate synapse, quantal amplitude does not decrease as the number of release sites increases with age [57]. In the future, it might be fruitful to investigate the effects of sensory deprivation on these synaptic parameters in different regions.

In many regions of the brain, chronic suppression of activity using pharmacological agents results in a dramatic upregulation of synaptic components, such as dendritic spines [58,59] or an increase in network activity [60]. These changes can be seen as homeostatic responses to the loss of active inputs. It is not known if pushing the activity levels of individual neurons beyond their normal operating range *in vivo*, in either the developing or the relatively mature brain can cause homeostatic changes. Molecular genetic tools that allow selective manipulation of single or small numbers of neurons will help to answer such questions.

There are also examples of specific naturally occurring mutations or deliberate genetic alterations that give rise to compensatory changes, some of which might share mechanisms with homeostatic plasticity. Recent studies in congenitally deaf mice have found an increase in the strength, primarily presynaptic, of the first synapse made by the auditory nerve fibers in the brain stem [61•]. In gerbils deafened by bilateral cochlear ablation, both an increase in excitatory and a decrease in inhibitory synaptic transmission were observed in the inferior colliculus [62]. Compensatory responses have also been documented in the mammalian neuromuscular junction (NMJ). For example, mice that are deficient in neuregulin have fewer acetylcholine receptors in the muscle, but an increase in the quantal content nearly equalizes the nerve-evoked response [63]. A recent study in mice that lack the synthetic enzyme for acetylcholine, which are therefore unable to sustain neurotransmitter release at the NMJ, noted an increase in the size of the acetylcholine receptor surface in the muscle, a potentially compensatory response [64]. Whether or not any of these phenomena have shared homeostatic mechanisms is unclear.

## Concluding remarks

There is now much evidence to suggest that when neuronal activity strays from a normal physiological range synaptic gain can be altered to regain normal activity. How exactly this is achieved is still not fully understood. In fact, there appears to be multiple ways to alter synaptic gain in the direction of homeostasis, including changes in pre- and postsynaptic properties, and in the number of synapses. It remains to be determined if these different ways of achieving synaptic homeostasis have shared mechanisms, and if they are related to other forms of plasticity. The ability to control activity of individual neurons using molecular genetic tools, while at the same time altering the expression of candidate genes in the same neurons, will greatly enable the study of the mechanisms involved in homeostatic plasticity. Finally, it is crucial to determine if this form of plasticity occurs in the intact brain *in vivo*.

## Update

Several additional studies of relevance have been published after the initial submission of this review. At the *Drosophila* neuromuscular junction, where homeostatic plasticity has been characterized extensively, Goodman and colleagues have found that CaMKII in the muscle is necessary to initiate retrograde signals that cause changes in the presynaptic boutons [65]. Roles for CaMKII isoforms, both α and β, in synaptic plasticity have also been suggested by recent studies in mammalian neurons grown in culture [66,67]. In hippocampal neurons, overexpression of CaMKIIβ, which is more abundant than CaMKIIα early in development, appears to increase dendritic morphology and synapse number early, but has no effect in older neurons [67]. By contrast, CaMKIIα, when constitutively active in young cortical neurons, leads to a reduction in synapse number and strengthening of the remaining synapses [66]. Together with previous reports, these new papers have made CaMKII an important candidate in the cascade of signals mediating homeostatic synaptic plasticity.

A recent study has shown that monocular deprivation during a critical period in rats results in long-term depression of synapses in the visual cortex [68], in apparent contrast to previous work reporting a homeostatic increase in synaptic strength using similar sensory deprivation [51••]. The contrasting results could be due to differences in the methods used to assess synaptic strengths, the types of synapses studied, or subtle differences in the developmental stage of animals used.

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This study used the inwardly rectifying potassium channel Kir2.1 to reduce activity selectively in single neurons in a network of normally active hippocampal neurons in culture. When activity was reduced before synapse formation, there was a competitive loss of synaptic inputs to the less active neuron. By contrast, when activity was reduced after most synapses had formed, there was a homeostatic increase in synaptic input.

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