Hebb and homeostasis in neuronal plasticity

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The positive-feedback nature of Hebbian plasticity can destabilize the properties of neuronal networks. Recent work has demonstrated that this destabilizing influence is counteracted by a number of homeostatic plasticity mechanisms that stabilize neuronal activity. Such mechanisms include global changes in synaptic strengths, changes in neuronal excitability, and the regulation of synapse number. These recent studies suggest that Hebbian and homeostatic plasticity often target the same molecular substrates, and have opposing effects on synaptic or neuronal properties. These advances significantly broaden our framework for understanding the effects of activity on synaptic function and neuronal excitability.

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Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionate
AMPAR	AMPA receptor
BDNF	brain-derived neurotrophic factor
CNQX	6-cyano-7-nitroquinoxaline-2,3-dione
LTD	long-term depression
LTP	long-term potentiation
NMDA	*N*-methyl-D-aspartate
NMDAR	NMDA receptor
TTX	tetrodotoxin

Introduction

In the quest to explain how the nervous system encodes information, neuroscientists have uncovered a bewildering array of cellular mechanisms by which experience can modify the properties of neuronal networks. Information transfer across a synapse is a complex process that depends on presynaptic release of neurotransmitter, transduction by postsynaptic receptors, and integration of many synaptic responses into a sequence of action potentials via voltage-gated ion channels. Nearly every phase of this process can exhibit activity-dependent plasticity, and often different experimental protocols produce seemingly contradictory effects on any given parameter of synaptic function. A principle that may help illuminate this contradictory literature is to view plasticity as occurring in two forms that can have diametrically opposite effects: Hebbian, correlation-based mechanisms that progressively modify network properties; and homeostatic mechanisms that promote network stability.

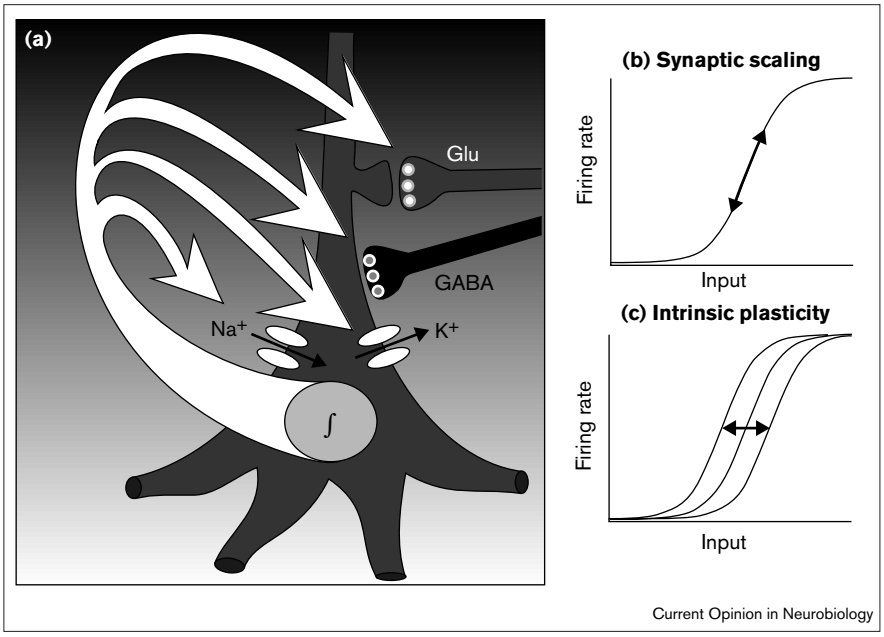
These two forms of plasticity are opposite sides of the same coin. Correlation-based plasticity, such as long-term potentiation (LTP) and long-term depression (LTD), is thought to be crucial for information storage because it produces associative changes in the strength of individual synaptic connections. Such plasticity is prone to instability, however, so LTP and LTD are probably insufficient to explain activity-dependent development and learning. Correlation-based learning rules are unstable because once a synaptic input is potentiated it becomes easier for the presynaptic neuron to depolarize the postsynaptic neuron and make it fire, and this promotes further potentiation of that synapse. In addition, potentiation of some inputs will increase the net excitatory synaptic drive to the postsynaptic neuron, making it easier for other inputs to depolarize the neuron and promoting potentiation of previously ineffective synapses. In order to harness the ability of Hebbian mechanisms to selectively modify synaptic connectivity, there must be additional learning rules that stabilize the properties of neuronal networks.

In principle, a number of mechanisms are capable of stabilizing activity when synapse number and strength are changing dramatically. For example, the cycle of increasing correlation produced by synaptic potentiation would be short-circuited by any mechanism that stabilized postsynaptic firing rates [1,2]. An alternative mechanism would be to raise the threshold for LTP and lower the threshold for LTD as postsynaptic activity rises, so that LTD would be promoted and synaptic strengths would fall again [3]. A wealth of experimental evidence is now beginning to accumulate that suggests that these and other strategies are employed by central networks to maintain stability of network function; in addition, it is becoming clear that most targets of Hebbian plasticity are also regulated in a homeostatic manner. Importantly, both the mechanisms and substrates of these two forms of plasticity share important components, suggesting that they may be inextricably intertwined at the molecular level. In this review, we discuss recent advances in our understanding of homeostatic plasticity in central networks, and its mechanistic and functional relationship to Hebbian plasticity.

Conservation of activity levels in neuronal networks

It has now been established in a number of systems that networks of neurons can adapt to changing activity patterns by altering the level of synaptic transmission or the array of voltage-dependent conductances expressed by component neurons. For example, in both invertebrate central pattern generators and vertebrate spinal networks, pharmacological blockade of rhythmic activity engages compensatory mechanisms that cause activity to resume after a period of hours to days [4–6]. Similarly, chronically reducing inhibition in cortical networks initially raises firing rates, but over a period of days, firing rates return to

Figure 1



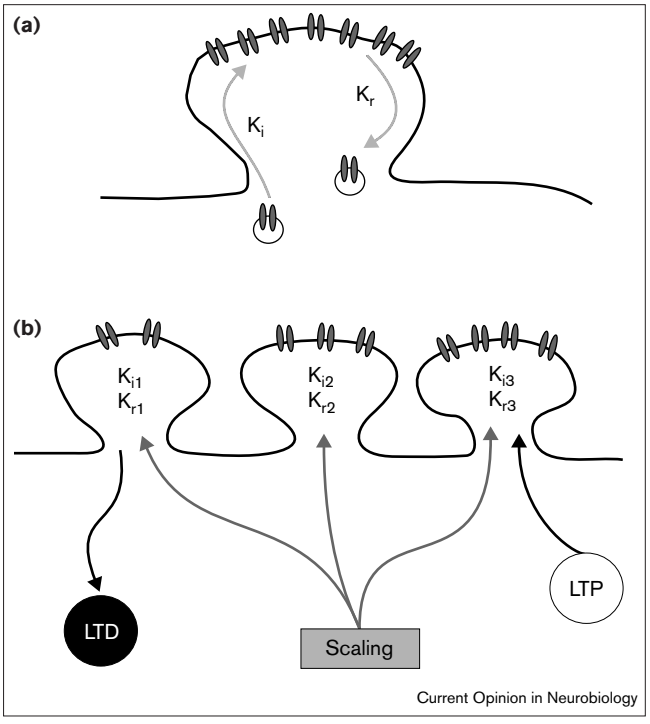
(a) Homeostatic plasticity uses some measure of activity (such as integrating average firing rate over some long time scale, indicated by the integral sign) to adjust excitatory and inhibitory synaptic strengths, as well as the voltage-dependent conductances (Na^+ and K^+) that control neuronal firing properties. These two forms of homeostatic plasticity are likely to have different functions in cortical networks. **(b)** By scaling the strength of all of a neuron's inputs up or down ('synaptic scaling'), a neuron's properties can be shifted up or down its input/output curve; this determines how fast the neuron fires for a given amount of synaptic drive. Excitatory and inhibitory inputs can be regulated independently, which allows neurons (and circuits) to adjust the balance of excitation and inhibition in an activity-dependent way. **(c)** In contrast, regulation of intrinsic conductances ('intrinsic plasticity') can modify the input/output curve of the neuron, by shifting it left (so it will fire less for a given level of synaptic drive) or right (so that it will fire more for a given level of synaptic drive) and can also modify the slope of this curve. Intrinsic plasticity will therefore change the sensitivity of a neuron to both excitatory and inhibitory inputs, suggesting that this is a general mechanism for allowing neurons to maximize the detection of whatever input they do receive. Glu, glutamate.

control levels [7]. These experiments suggest that neurons and networks have some 'set-point' of activity that is dynamically maintained. The exact feature of activity that is being conserved is unclear: it could be average firing rate, average calcium concentration, or some more subtle statistical measure of network activity. What is clear is that many aspects of network function can be modulated to maintain this set-point, including the strength of excitatory and inhibitory connections, and the intrinsic excitability of individual neurons (Figure 1) [2,7,8,9••]. This review will focus on changes in excitatory synapse strength and number, and on changes in intrinsic excitability.

Synaptic scaling

One mechanism that could help maintain relatively constant activity levels is if neurons increased the strength of all excitatory connections in response to a prolonged drop in firing rates, and *vice versa*. Such bi-directional plasticity of AMPA-mediated glutamatergic synaptic currents has recently been demonstrated in cultured cortical and spinal networks, and occurs through a scaling up or down of the strength of all of a neuron's excitatory inputs [7,8]. This form of plasticity, termed 'synaptic scaling', has both interesting differences and similarities to more intensively studied forms of plasticity such as LTP. Whereas LTP can be induced rapidly, synaptic scaling requires hours to days of altered activity to produce measurable changes in synaptic strength, suggesting that synaptic scaling responds to an activity signal that is integrated over long time-scales [7,8]. LTP depends on NMDA receptor (NMDAR) activation, but synaptic scaling does not [7,8]. AMPA receptor (AMPAR) activation is probably not necessary for LTP induction beyond its role in depolarizing the postsynaptic neuron, but the role of AMPAR activation in synaptic scaling is less clear. Blockade of spiking with tetrodotoxin (TTX), which indirectly reduces AMPAR activation, and blockade of AMPARs with CNQX, which indirectly eliminates spiking, both scale up synaptic currents, but it is not clear whether this is attributable to reducing activity or reducing activation of AMPARs [7,8]. Recent experiments in cortical networks suggest that bi-directional synaptic scaling can occur even when AMPARs and NMDARs are blocked, suggesting that the important signal is some function of postsynaptic activity [10]. Perhaps the most important difference between LTP and synaptic scaling is that, rather than operating in a synapse-specific manner, synaptic scaling occurs through a multiplicative scaling up or down of all of a neuron's synaptic strengths [7]. This feature may allow synaptic scaling to regulate the total synaptic strength of a neuron, while preserving relative differences in strength between individual synaptic inputs.

Figure 2



Activity and AMPAR trafficking: global and local receptor regulation. **(a)** The number of AMPARs clustered at a synaptic site is the result of an equilibrium between insertion (Ki) and removal (Kr) of receptors. This cycling is highly regulated and involves many binding and scaffolding proteins, as well as endocytotic and exocytotic machinery. **(b)** Recent data suggest that LTP and LTD can result in rapid and local changes in AMPAR number, perhaps by selectively targeting the insertion or removal processes. Synaptic scaling also occurs through changes in the number of receptors clustered at synapses, but acts globally at all synaptic sites and over much slower time scales. This suggests that AMPAR turnover can be regulated by activity on both local and global spatial scales, and at both fast and slow temporal scales.

Activity and AMPAR trafficking: global and local receptor regulation

While the differences between LTP/LTD and synaptic scaling are profound, there are also interesting similarities. The preponderance of evidence to date suggests that synaptic scaling and at least some forms of LTP/LTD are expressed as changes in the number of postsynaptic AMPARs clustered at synapses. Tetanic stimulation in hippocampal and thalamocortical slices can convert developing synapses in which only NMDA currents are present into synapses in which both NMDA and AMPA currents can be identified — possibly through the insertion of new AMPARs into the postsynaptic membrane [11,12]. By analogy, LTP of adult synapses may also occur through insertion or recruitment of new AMPARs into functional synaptic sites (Figure 2). This interpretation has been supported by recent experiments showing that green fluorescent protein (GFP)-tagged AMPARs are mobilized into spines following tetanic stimulation, and that some of these receptors are detectable on the postsynaptic membrane [13••]. In addition, LTD protocols can rapidly reduce the number of synapses immunopositive for AMPARs [14••].

A number of other recent studies have suggested that AMPARs can be rapidly inserted into or removed from the postsynaptic membrane. When proteins known to inhibit presynaptic membrane fusion events are infused into a postsynaptic neuron, AMPA-mediated synaptic transmission and the surface expression of AMPARs is rapidly reduced [15,16,17••]. Conversely, enhancing membrane fusion events rapidly increases AMPA synaptic currents, and this enhancement is occluded by LTP [18]. As well as suggesting that LTP and LTD occur through the rapid insertion and removal of AMPARs, these studies have raised the interesting possibility that AMPAR turnover at central synapses may be quite rapid. Although compelling, these studies should be interpreted with caution, as our understanding of the molecular events that underlie postsynaptic membrane trafficking and AMPAR turnover is minimal at best. Interfering with the membrane fusion machinery could influence synaptic transmission in a variety of indirect ways, and it is not clear what the relationship is between the rapid synaptic changes seen in many (but not all) of these studies and 'constitutive' receptor turnover.

Homeostatic plasticity also appears to operate through changes in the number of postsynaptic receptors, but over much longer time scales (Figure 2). Scaling up of synaptic currents in response to reduced activity is accompanied by an increase in the postsynaptic responsiveness to glutamate agonists [7,8], an increase in AMPAR half-life and the number of receptors detectable at synaptic sites [8], and an increase in the number of channels that open in response to glutamate application [19]. This increased accumulation of receptors at synapses could result from a cell-wide increase in insertion rates (or decrease in removal rates), suggesting that slow, 'constitutive' receptor turnover may actually be a highly regulated process. Alternatively, receptors could accumulate because of a net increase in the number of available AMPAR binding sites, due to changes in the number or availability of synaptic scaffolding proteins. Taken together with data on rapid regulation of AMPARs, these studies suggest that the processes that determine the number of glutamate receptors clustered at synapses are subject to regulation on both rapid and slow temporal scales, and both local and global spatial scales. Whether these two forms of plasticity target the same sites in the receptor cycling machinery remains to be seen.

Activity-dependent regulation of neuronal excitability

Most studies of plasticity underlying learning and development have focused on changes in synaptic strength. But another potential substrate for activity-dependent plasticity is the rich array of voltage-dependent sodium,

potassium, and calcium conductances that neurons express. The mixture and distribution of these conductances determines the integrative properties of the postsynaptic neuron, suggesting that if activity could selectively regulate the expression of these conductances, the postsynaptic responsiveness of a neuron to its inputs could be dramatically altered. Work on invertebrate neurons has suggested that ongoing patterned activity can indeed regulate the expression of voltage-dependent conductances [20,21,22••,23]. A similar phenomenon has now been demonstrated in cultured neocortical pyramidal neurons. Prolonged activity blockade lowers the threshold for spike generation, and neurons fire at a higher frequency for any given level of current injection [9••]. This occurs through selective modifications in the magnitude of voltage-dependent currents: sodium currents increase, persistent potassium currents decrease, whereas calcium currents and transient potassium currents are unaltered. The time-scale of this process is of the right order (i.e. hours to days) to contribute to the homeostatic regulation of firing rates demonstrated in these cultured cortical networks. In theory, the ability of activity to selectively modify the balance of inward and outward ion channels could serve a number of important functions, including fine-tuning the output properties of neurons to match the properties of their inputs [24], and regulating synaptic plasticity by contributing to local dendritic depolarization or by gating backpropagating action potentials [25,26].

Is there a non-homeostatic counterpart to the homeostatic regulation of intrinsic excitability? A recent study on deep cerebellar nuclei neurons suggests that there may be [27••]. Tetanization of inputs to these neurons produces a rapid and long-lasting increase in intrinsic excitability that depends on NMDAR activation. Interestingly, this could give rise to heterosynaptic interactions in which tetanization of one input increases the responsiveness of the neuron to all of its inputs. These recent studies suggest that both homeostatic and non-homeostatic plasticity of intrinsic excitability may play important and under-appreciated roles in developmental plasticity and information storage.

Activity-dependent regulation of synapse number

Might some forms of plasticity be expressed as changes in synapse number as well as changes in synapse strength? For both homeostatic and Hebbian forms of plasticity this issue has been controversial, and results from different investigators have varied widely. Prolonged changes in activity in hippocampal cultures, for example, have been reported to selectively modify the number of synaptic sites that express NMDARs but not AMPARs [28], or AMPARs but not NMDARs [29], whereas a recent study reports that selective blockade of AMPARs or NMDARs increases the number of AMPA-containing or NMDA-containing synaptic sites, respectively [30]. Although the results of these studies differ, they have all concluded that AMPARs and NMDARs are regulated independently. In apparent contrast to these anatomical studies on the number of immunopositive sites, electrophysiological studies in cortical cultures have found that AMPA and NMDA currents are increased or decreased proportionally by long-lasting changes in activity [19]. In addition, the amplitude of AMPA and NMDA currents are tightly correlated across a neuron's synapses [19,31], suggesting that if NMDARs and AMPARs are regulated independently over short time-scales (as predicted by most postsynaptic models of LTP and LTD), then there must be longer-acting mechanisms that slowly restore a fixed ratio of receptor types. While these studies suggest that activity may regulate the number and composition of functional synaptic sites, further work is needed in order to clarify under what conditions AMPARs and NMDARs are regulated independently and under what conditions they are regulated in parallel.

Similarly, studies examining the effects of activity on spine number in hippocampal slices have reached seemingly contradictory conclusions. Blockade of synaptic transmission for several hours in acutely cut slices causes an increase in spine number relative to slices that are electrically stimulated [32••]. In contrast, blockade of AMPARs with CNQX for several weeks in organotypic slices causes a loss of spines [33••]. These data suggest that on shorter time-scales, loss of synaptic activation may lead to spine generation in an attempt to compensate for lost excitatory input, but that when spines are inactive for long enough, they are retracted and lost.

The role of new synapse formation in LTP has long been controversial. LTP does not significantly increase the total number of spines on neurons [34], but recent papers using two-photon laser-scanning confocal microscopy to image spines in living tissue have found that LTP protocols cause sprouting of new spines near the site of potentiation [35,36••]. The role of these new spines in synaptic transmission is unclear, as the number of new spines is small and they do not appear to contribute to the potentiation produced by LTP [36••]. These new spines may be a way of generating additional 'synaptic substrate' once plasticity at available spines has been saturated, or may be a site of longer-term memory formation that is consolidated as a change in synapse number. Collectively, the studies described above suggest that the regulation of synapse number, like the regulation of synapse strength, may be complex and involve several opposing processes. Synapse number may increase locally following LTP, yet such increases may be opposed by homeostatic processes that act to globally adjust synapse number. While still speculative, such a process could foster a re-distribution of synaptic contacts so that increasing the number of connections at one site competitively decreases the number of connections elsewhere. Some such competitive process is a necessary counterpart to Hebbian mechanisms in order to explain the developmental retraction of synapses that occur during processes such as ocular dominance column formation [1,37].

Brain-derived neurotrophic factor and activity-dependent plasticity

The neurotrophin brain-derived neurotrophic factor (BDNF) may soon exceed calcium in the diversity of roles it has been postulated to play in the activity-dependent plasticity of central networks. Acutely, BDNF has been reported to modulate synaptic transmission and LTP [38–42,43••] and to directly depolarize postsynaptic neurons [44,45••], while longer exposures to BDNF regulate dendritic outgrowth [46], synaptic scaling of excitatory inputs [47], and intrinsic neuronal excitability [48••]. Interestingly, the short-term and long-term effects of BDNF at central synapses appear to work in opposite directions. Brief exposure to high concentrations of BDNF enhances excitatory synaptic transmission in some studies [38,39,41,42], increases short-term facilitation and reduces synaptic fatigue [39,49], and may also reduce inhibition [50,51]. Because BDNF production and release are activity-dependent, this suggests that the acute synaptic effects of BDNF could foster a positive-feedback cycle of synaptic enhancement.

In contrast, long-term exposure to low concentrations of BDNF appears to stabilize the activity of cortical networks by balancing the strength of excitatory and inhibitory inputs, and regulating intrinsic excitability [47,48••,52]. The model that has emerged from this work is that when activity falls and BDNF levels are reduced, excitatory inputs to pyramidal neurons are scaled up in strength, inhibitory inputs are reduced, and intrinsic excitability is increased. These factors act synergistically to raise pyramidal neuron firing rates. Conversely, when activity and BDNF levels rise, excitatory inputs to pyramidal neurons are scaled down while those onto interneurons are scaled up. This shifts the balance of activity in the network to favor inhibition and reduces pyramidal neuron firing rates. These data suggest that the acute destabilizing effects of BDNF are counteracted by a longer-term homeostatic readjustment of synaptic strengths. In contrast to data from cortical cultures, long-lasting exposure to BDNF increases the strengths of excitatory autaptic synapses in hippocampal single-neuron cultures [53]. This discrepancy could reflect a difference in the prior developmental history of the neurons: in single-neuron cultures, spontaneous activity is low and exposure to endogenous BDNF may be minimal. Alternatively, the net effect of BDNF treatment in hippocampus and neocortex may differ, perhaps because of differences in the relative importance of homeostatic and destabilizing plasticity in these different brain regions.

How can BDNF serve such a diversity of functions? The answer to this question is still unclear, and will probably remain so until we have a much better understanding of exactly when and where BDNF is released, how far it diffuses, and the effective concentrations that are achieved during particular patterns of activity. One point that is quite clear, however, is that experimentally disentangling the many actions of BDNF is a difficult enterprise. The effects of adding or removing BDNF from a network are likely to depend on the concentration used, the length of exposure or removal, the pattern of activation of the high-affinity receptor for BDNF, TrkB, and perhaps the prior developmental history. Some effects will be direct, whereas others may arise indirectly from changes in connectivity or in the balance of excitation and inhibition within the network. Interpreting the effects on synaptic plasticity of BDNF or TrkB knock-outs [40,43••] or of BDNF overexpression [54] is especially difficult, as even targeted mutations act over temporal and spatial windows that are broad enough to influence many properties of cortical or hippocampal networks.

Conclusions

Evidence is mounting that many properties of central networks can be regulated in a homeostatic manner by long-lasting changes in activity. Recent work suggests that homeostatic plasticity can target both ionotropic glutamate receptors to regulate synaptic strength, and voltage-dependent ion channels to regulate neuronal excitability; it can also modulate the number of synaptic connections that neurons receive. Interestingly, each of these targets of homeostatic plasticity are also thought to be regulated by correlation-based Hebbian mechanisms, suggesting that different aspects of activity exert opposing forces on synapse strength, intrinsic excitability, and synapse number. An important challenge for the future is to disentangle the functional and mechanistic differences between these two plasticity mechanisms, and to begin to understand how they cooperate during learning and development to fine-tune the properties of neuronal networks.

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