

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
AMPA	AMPA receptor
BDNF	brain-derived neurotrophic factor
CNQX	6-cyano-7-nitroquinoxaline-2,3-dione
LTD	long-term depression
LTP	long-term potentiation
NMDA	<i>N</i> -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.

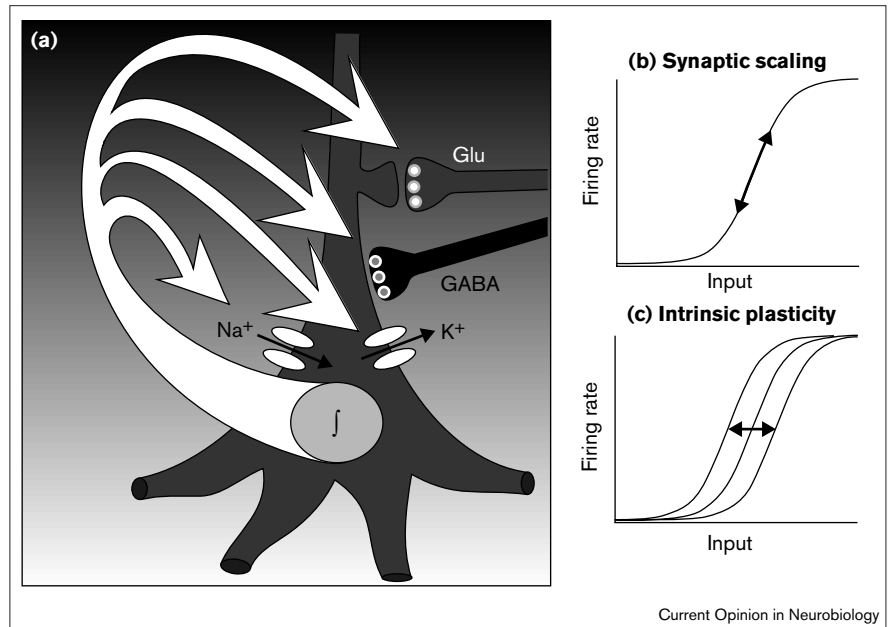
In principle, a number of mechanisms are capable of stabilizing activity when synapse number and strength are changing dramatically. For example, the cycle of increasing correlation produced by synaptic potentiation would be short-circuited by any mechanism that stabilized postsynaptic firing rates [1,2]. 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.



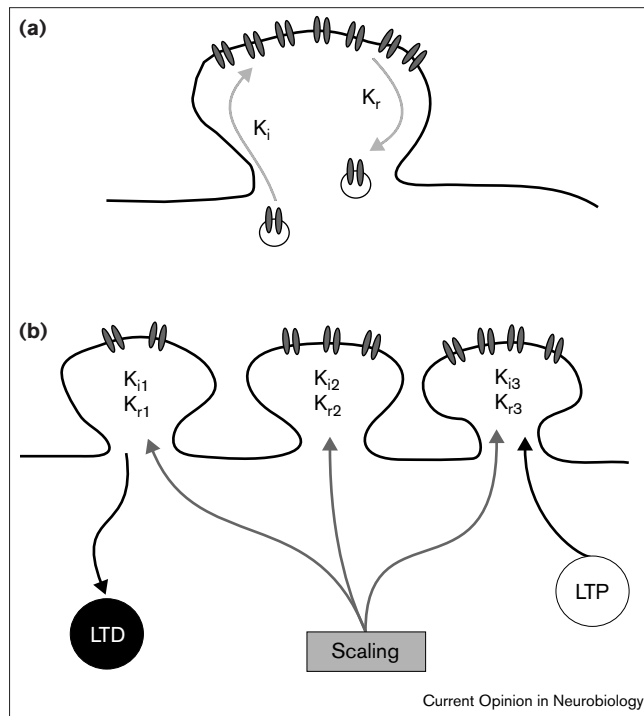
control levels [7]. These experiments suggest that neurons and networks have some 'set-point' of activity that is dynamically maintained. The exact feature of activity that is being conserved is unclear: it could be average firing rate, average calcium concentration, or some more subtle statistical measure 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 (AMPA) 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 (K_i) and removal (K_r) 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 longer 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.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
 - of outstanding interest
1. Miller KD: **Synaptic economics: competition and cooperation in synaptic plasticity.** *Neuron* 1996, **17**:371-374.
 2. Turrigiano GG: **Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same.** *Trends Neurosci* 1999, **22**:221-228.
 3. Bear, MF: **Mechanism for a sliding synaptic modification threshold.** *Neuron* 1995, **15**:1-4.
 4. Chub N, O'Donovan MJ: **Blockade and recovery of spontaneous rhythmic activity after application of neurotransmitter antagonists to spinal networks of the chick embryo.** *J Neurosci* 1998, **18**:294-306.
 5. Thoby-Brisson M, Simmers J: **Neuromodulatory inputs maintain expression of a lobster motor pattern-generating network in a modulation-dependent state: evidence from long-term decentralization in vitro.** *J Neurosci* 1998, **18**:2212-2225.
 6. Golowasch J, Casey M, Abbott LF, Marder E: **Network stability from activity-dependent regulation of neuronal conductances.** *Neural Comput* 1999, **11**:1079-1096.
 7. Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB: **Activity-dependent scaling of quantal amplitude in neocortical neurons.** *Nature* 1998, **391**:892-895.

8. O'Brien R, Kambol S, Ehlers MD, Rosen KR, Kischback GD, Huganir RL: **Activity-dependent modulation of synaptic AMPA receptor accumulation.** *Neuron* 1998, **21**:1067-1078.

9. Desai NS, Rutherford LC, Turrigiano GG: **Plasticity in the intrinsic excitability of cortical pyramidal neurons.** *Nat Neurosci* 1999, **2**:515-520.

Using dissociated cultures from postnatal cortex, the authors show that long-lasting changes in activity can modify the excitability of pyramidal neurons. Activity blockade for 48 hours lowered the spike threshold and increased the firing rate by selective modification of the magnitudes of voltage-dependent conductances. This study demonstrates that activity-dependent plasticity of central circuits can operate not only on the ionotropic receptors underlying synaptic transmission, but also on the voltage-dependent ion channels that determine the firing and integrative properties of a neuron.

10. Leslie KR, Nelson SB, Turrigiano GG: **Postsynaptic depolarization scales quantal amplitudes in cortical cultures.** *Soc Neurosci Abstr* 1999, **25**:793.2.

11. Liao D, Hessler NA, Malinow R: **Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice.** *Nature* 1995, **375**:400-404.

12. Isaac JTR, Nicoll RA, Malenka RC: **Evidence for silent synapses: implications for the expression of LTP.** *Neuron* 1995, **15**:427-434.

13. Shi SH, Hayashi Y, Petralia RS, Zaman SH, Wenthold RJ, Svoboda K, Malinow R: **Rapid spine delivery and redistribution of AMPA receptors after synaptic NMDA receptor activation.** *Science* 1999, **284**:1811-1816.

The authors used two-photon laser-scanning confocal microscopy to visualize green fluorescent protein-tagged AMPA receptors that were overexpressed in organotypic hippocampal cultures. Following tetanic stimulation, the tagged receptors were redistributed into dendritic spines. Some of the fluorescence associated with these receptors was detectable on the spine surface following tetanization, suggesting that this stimulation protocol causes insertion of AMPA receptors into the postsynaptic membrane.

14. Carroll RC, Lissen DV, von Zastrow M, Nicoll RA, Malenka RC: **Rapid redistribution of glutamate receptors contributes to long-term depression in hippocampal cultures.** *Nat Neurosci* 1999, **2**:454-460.

Using field stimulation to induce LTD at large numbers of synapses in dissociated hippocampal cultures, the authors show that LTD is associated with a reduction in the amplitude of miniature excitatory synaptic currents, and in the number of synaptic sites that are immunopositive for AMPA receptors. No effect was found on the number of synaptic sites immunopositive for NMDA receptors.

15. Nishimue A, Isaac JTR, Molnar E, Neol J, Nash SR, Tagaya M, Collingridge GL, Nakanishi S, Henley JM: **NSF binding to GluR2 regulates synaptic transmission.** *Neuron* 1998, **21**:87-97.

16. Noel J, Ralph S, Pickard L, Williams J, Molnar E, Uney JB, Collingridge GL, Henley JM: **Surface expression of AMPA receptors in hippocampal neurons is regulated by an NSF-dependent mechanism.** *Neuron* 1999, **23**:365-367.

17. Luthi A, Chittajallu R, Duprat F, Palmer MJ, Benke TZ, Kidd FL, Henley JM, Isaac JTR, Collingridge GL: **Hippocampal LTD expression involves a pool of AMPARs regulated by the NSF-GluR2 interaction.** *Neuron* 1999, **24**:389-399.

The authors infused into hippocampal postsynaptic neurons a peptide (pep2m) that interferes with AMPA receptor binding to NSF (*N*-ethylmaleimide-sensitive factor), a protein thought to be involved in membrane fusion events. This caused a decline in AMPA synaptic transmission that occludes LTD; in addition, prior induction of LTD at these synapses occluded the effects of infusion of pep2m. These data suggest that LTD targets a pool of AMPARs that are regulated by an NSF-AMPA interaction. This could be due to an effect of NSF on receptor cycling into and out of the postsynaptic membrane or to interference with some other step in receptor regulation.

18. Lledo PM, Zhang X, Sudhof TC, Malenka RC, Nicoll RA: **Postsynaptic membrane fusion and long-term potentiation.** *Science* 1998, **279**:399-403.

19. Watt AJ, van Rossum MCW, McLeod KM, Nelson SB, Turrigiano GG: **Activity co-regulates quantal AMPA and NMDA currents at neocortical synapses.** *Neuron* 2000, in press.

20. Turrigiano GG, Abbott LF, Marder E: **Activity changes the intrinsic properties of cultured neurons.** *Science* 1994, **264**:974-976.

21. Turrigiano G, Le Masson G, Marder E: **Selective regulation of current densities underlies spontaneous changes in the activity of cultured neurons.** *J Neurosci* 1995, **15**:3640-3652.

22. Golowasch J, Abbott LF, Marder E: **Activity-dependent regulation of potassium currents in an identified neuron of the stomatogastric ganglion of the crab *Cancer borealis*.** *J Neurosci* 1999, **19**:RC33.

In this manuscript, the authors show that continuous stimulation of intact stomatogastric ganglion neurons for several hours can alter the magnitude of potassium currents. The effects of this stimulation depend on both the identity of the neuron and the identity of the current: in some neurons, this stimulation has no effect, whereas in others, some currents are increased, some are decreased, and some are unaltered. These data suggest that ongoing activity can continuously modify the magnitude of ionic conductances and that these effects can be quite complex.

23. Hong SJ, Lnenicka GA: **Characterization of a P-type calcium current in a crayfish motoneuron and its selective modulation by impulse activity.** *J Neurophysiol* 1997, **77**:76-85.

24. Stemmler M, Koch C: **How voltage-dependent conductances can adapt to maximize the information encoded by neuronal firing rate.** *Nat Neurosci* 1999, **2**:521-527.

25. Hoffman DA, Magee JC, Colbert CM, Johnston D: **K⁺ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons.** *Nature* 1997, **387**:869-875.

26. Magee JC, Johnston D: **Synaptic activation of voltage-gated channels in the dendrites of hippocampal pyramidal neurons.** *Science* 1995, **268**:301-304.

27. Aizenman CD, Linden DJ: **Rapid, synaptically-driven increases in the intrinsic excitability of cerebellar deep nuclear neurons.** *Nat Neurosci* 2000, **3**:109-111.

The authors demonstrate that tetanization of inputs to deep cerebellar nuclear neurons rapidly increases the intrinsic excitability of these neurons, so that spike threshold is reduced and the neurons fire faster for a given level of current injection. This effect was dependent on NMDA-receptor-mediated transmission, but could also be induced without synaptic activation by direct depolarization of the postsynaptic neuron. These data suggest that strong activation of one set of inputs may sensitize the neuron to all synaptic inputs.

28. Rao A, Craig AM: **Activity regulates the synaptic localization of the NMDA receptor in hippocampal neurons.** *Neuron* 1997, **19**:801-812.

29. Lissin DV, Gomperts SN, Carroll RC, Christine CW, Kalman D, Kitamura M, Hardy S, Nicoll RA, Malenka RC, von Zastrow M: **Activity differentially regulates the surface expression of synaptic AMPA and NMDA glutamate receptors.** *Proc Natl Acad Sci USA* 1998, **95**:7097-7102.

30. Liao D, Zhang X, O'Brien R, Ehlers MD, Huganir RL: **Regulation of morphological postsynaptic silent synapses in developing hippocampal neurons.** *Nat Neurosci* 1999, **2**:37-43.

31. Umeyama M, Senda M, Murphy TH: **Behavior of NMDA and AMPA receptor mediated miniature EPSCs at synapses identified by calcium imaging.** *Soc Neurosci Abstr* 1999, **25**:399.4.

32. Kirov SA, Harris KM: **Dendrites are more spiny on mature hippocampal neurons when synapses are inactivated.** *Nat Neurosci* 1999, **2**:878-883.

The authors use confocal microscopy to quantify the density of spines on Dil (styryl dye)-labeled neurons from acutely cut hippocampal slices. They compared spine density from slices in which synaptic transmission was blocked to that from slices that were stimulated electrically for several hours. Synaptic blockade produced a 30% increase in spine density relative to stimulated slices.

33. McKinney RA, Capogna M, Durr R, Gähwiler BH, Thompson SM: **Miniature synaptic events maintain dendritic spines via AMPA receptor activation.** *Nat Neurosci* 1999, **2**:44-49.

Using organotypic hippocampal slices, the authors show that long-term (several weeks) blockade of AMPA receptors causes a loss of dendritic spines in CA1 pyramidal neurons, while blockade with TTX does not affect spine number. Spine loss was also caused by transection of Schaffer collaterals, and this loss could be prevented by direct application of AMPA. These data suggest that long-term spine maintenance is dependent on activation of AMPA receptors, and that spontaneous release of glutamate is sufficient for this maintenance.

34. Sorra KE, Harris KM: **Stability in synapse number and size at 2 hr after long-term potentiation in hippocampal area CA1.** *J Neurosci* 1998, **18**:658-671.

35. Maletic-Savatic M, Malinow R, Svoboda K: **Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity.** *Science* 1999, **283**:1923-1927.

36. Engert F, Bonhoeffer T: **Dendritic spine changes associated with •• hippocampal long-term synaptic plasticity.** *Nature* 1999, **399**:66-70. In these experiments, the authors locally induce LTP along a small segment of dendrite (with LTP blocked elsewhere) and monitor the dendrite for changes in spine number. They find that new spines are selectively induced at the site of LTP induction, whereas spine number is unchanged in adjacent segments of dendrite. Spine induction is only seen when the LTP protocol successfully induces LTP, and is blocked by the NMDAR antagonist 2-amino-5-phosphovaleate (APV).
37. Shatz CJ: **Impulse activity and the patterning of connections during CNS development.** *Neuron* 1990, **5**:745-756.
38. Kang H, Schuman EM: **Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus.** *Science* 1995, **267**:1658-1662.
39. Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B: **Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus.** *Nature* 1996, **381**:706-709.
40. Korte M, Staiger V, Griesbeck O, Thoenen H, Bonhoeffer T: **The involvement of brain-derived neurotrophic factor in hippocampal long-term potentiation revealed by gene targeting experiments.** *J Physiol (Paris)* 1996, **90**:157-164.
41. Akaneya Y, Tsumoto T, Hatanaka H: **Brain-derived neurotrophic factor enhances long-term potentiation in rat visual cortex.** *J Neurophysiol* 1997, **76**:4198-4201.
42. Carmignoto G, Pizzorusso T, Tia S, Vicini S: **BDNF and NGF potentiate excitatory synaptic transmission in the rat visual cortex.** *J Physiol* 1997, **498**:153-164.
43. Minichiello L, Korte M, Wolfner D, Kuhn K, Unkicker K, Cestari V, Rossi •• Arnaud C, Lipp H-P, Bonhoeffer T, Klein R: **Essential role for TrkB receptors in hippocampus-mediated learning.** *Neuron* 1999, **24**:401-414.
- Using a CNS-targeted knockout of TrkB receptors that occurs postnatally, the authors assess the effects of TrkB loss on hippocampal LTP and spatial memory tasks. Homozygotes show an almost complete loss of LTP and are impaired in spatial memory tasks. Interestingly, heterozygotes show a significant reduction in LTP that is almost as severe as the homozygotes, yet show no behavioral impairments. These data suggest either that very low levels of LTP are sufficient for spatial memory or that there is a strong dissociation between LTP and spatial memory.
44. Li H-S, Xu X-ZS, Montell C: **Activation of a TRPC3-dependent cation current through the neurotrophin BDNF.** *Neuron* 1999, **24**:261-273.
45. Kafitz KW, Rose CR, Thoenen H, Konnerth A: **Neurotrophin-evoked •• rapid excitation through TrkB receptors.** *Nature* 1999, **401**:918-921. This paper (see also [44]) expands the already significant array of effects BDNF can have on central neurons by demonstrating that brief puffs of

BDNF can directly depolarize a variety of central neurons. This effect is rapid (milliseconds) – too fast to be mediated by the receptor tyrosine kinase phosphorylation thought to underlie most other effects of BDNF. This effect is only seen with high concentrations of BDNF (greater than 20 ng/ml), and does not appear to saturate at concentrations (100–200 ng/ml) at which other effects of BDNF saturate.

46. McAllister AK, Lo DC, Katz LC: **Neurotrophins regulate dendritic growth in developing visual cortex.** *Neuron* 1995, **15**:791-803.
47. Rutherford LC, Nelson SB, Turrigiano GG: **Opposite effects of BDNF on the quantal amplitude of pyramidal and interneuron excitatory synapses.** *Neuron* 1998, **21**:521-530.
48. Desai NS, Rutherford LC, Turrigiano GG: **BDNF regulates the •• intrinsic excitability of cortical neurons.** *Learn Memory* 1999, **6**:284-291.
- The authors have demonstrated previously that long-lasting changes in activity produce homeostatic changes both in excitatory synaptic strengths [7] and in the intrinsic excitability of cultured neocortical neurons [9**], and that these synaptic changes are mediated through the activity-dependent release of BDNF [47]. Here, they show that the changes in intrinsic excitability produced by activity blockade are also mediated by BDNF. Application of BDNF during the period of activity deprivation prevented – while preventing endogenously released BDNF from activating TrkB receptors mimicked – the effects of activity blockade. This suggests that BDNF produces coordinated changes in intrinsic and synaptic properties that act synergistically to regulate firing rates.
49. Gottschalk W, Pozzo-Miller LT, Figurov A, Lu B: **Presynaptic modulation of synaptic transmission and plasticity by brain-derived neurotrophic factor in the developing hippocampus.** *J Neurosci* 1998, **18**:6830-6839.
50. Tanaka T, Saito H, Matsuki N: **Inhibition of GABA_A synaptic responses by brain-derived neurotrophic factor (BDNF) in rat hippocampus.** *J Neurosci* 1997, **17**:2959-2966.
51. Frerking M, Malenka RC, Nicoll RA: **Brain-derived neurotrophic factor (BDNF) modulates inhibitory, but not excitatory, transmission in the CA1 region of the hippocampus.** *J Neurophysiol* 1998, **80**:3383-3386.
52. Rutherford LC, DeWan A, Lauer H, Turrigiano GG: **BDNF mediates the activity-dependent regulation of inhibition in neocortical cultures.** *J Neurosci* 1997, **17**:4527-4535.
53. Sherwood NT, Lo DC: **Long-term enhancement of central synaptic transmission by chronic BDNF treatment.** *J Neurosci* 1999, **19**:7025-7036.
54. Huang ZJ, Kirkwood A, Pizzorusso T, Porciatti V, Morales B, Bear MF, Maffei L, Tonegawa S: **BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex.** *Cell* 1999, **98**:1-20.