Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same

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During learning and development, neural circuitry is refined, in part, through changes in the number and strength of synapses. Most studies of long-term changes in synaptic strength have concentrated on Hebbian mechanisms, where these changes occur in a synapse-specific manner. While Hebbian mechanisms are important for modifying neuronal circuitry selectively, they might not be sufficient because they tend to destabilize the activity of neuronal networks. Recently, several forms of homeostatic plasticity that stabilize the properties of neural circuits have been identified. These include mechanisms that regulate neuronal excitability, stabilize total synaptic strength, and influence the rate and extent of synapse formation. These forms of homeostatic plasticity are likely to go 'hand-in-glove' with Hebbian mechanisms to allow experience to modify the properties of neuronal networks selectively.

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NERVOUS SYSTEMS are subject to two opposing requirements: the need for change and the need for stability. Change, in the form of activity-dependent alterations in the number and strength of synaptic connections, allows the properties of neuronal circuits to be refined by experience[1–3]. Many forms of activity-dependent plasticity exist and this diversity raises an important question: given the variety of mechanisms that promote change, how do neuronal networks maintain some degree of constancy in their basic properties? The answer that is emerging from recent work is that as experience-dependent plasticity changes the activity patterns of the network, several forms of homeostatic plasticity are engaged that act to restore stability to network function. Experience-dependent plasticity is thus composed of two opposing but complementary forces: one that modifies neuronal circuits progressively by creating selective differences between individual elements and another that regulates circuit properties to stabilize the overall activity of the network.

Historically, most experimental efforts aimed at identifying the biological substrates of experience-dependent plasticity have concentrated on Hebbian synaptic plasticity, where correlated firing between pre- and postsynaptic neurons leads to an increase in synaptic strength and uncorrelated firing leads to synaptic weakening[1–6]. Hebbian rules for the use-dependent modification of synaptic strengths are extremely powerful. They constitute the best-developed model of how information is stored in neural circuits[1,2,4–6] and how synaptic connections are refined during development[3,7,8]. However, Hebbian plasticity also has a 'dark side'. Hebbian rules for the change of synaptic strengths according to correlations in neuron firing are unstable[9–12] because as inputs are potentiated, the firing rate of the postsynaptic neuron rises, which increases the positive correlation between the neuron and its inputs. In turn, this produces more potentiation, and so on. As a result, inputs that are correlated positively increase to their limit, while inputs that are correlated negatively decrease to zero, and the selectivity of the network is lost. Developing networks face an analogous problem. Many developing neurons undergo a dramatic increase in the number of synaptic connections they receive. At the same time they must prevent firing rates from falling too low or rising too high, in order to remain responsive to their inputs and to allow activity to strengthen or weaken individual synaptic connections. Both of these tasks can be accomplished if the excitability of each neuron can be adjusted independently to keep firing rates within functional boundaries. This suggests that plasticity rules that serve to normalize activity could be important for allowing Hebbian plasticity to modify synaptic strengths selectively.

While the need for such plasticity rules has long been recognized[2,9–13], the nature of the biological mechanisms that generate this stability have remained elusive. Recent work from a number of systems, which range from the invertebrate neuromuscular junction (NMJ) to cortical circuits, has now begun to uncover an intriguing set of homeostatic mechanisms that promote stability in neuronal firing rates. These include mechanisms for adjusting the intrinsic excitability of neurons, mechanisms for adjusting synapse number and strength, and mechanisms for regulating Hebbian plasticity itself (recently reviewed by Bear[13]). This article will focus on recent work that has investigated the role of neuronal activity in the homeostatic regulation of intrinsic neuronal excitability, synaptic strengths and synapse stabilization.

Homeostasis of the intrinsic electrical properties of neurons

During the lifetime of a neuron, its electrical, morphological and synaptic properties fluctuate constantly.

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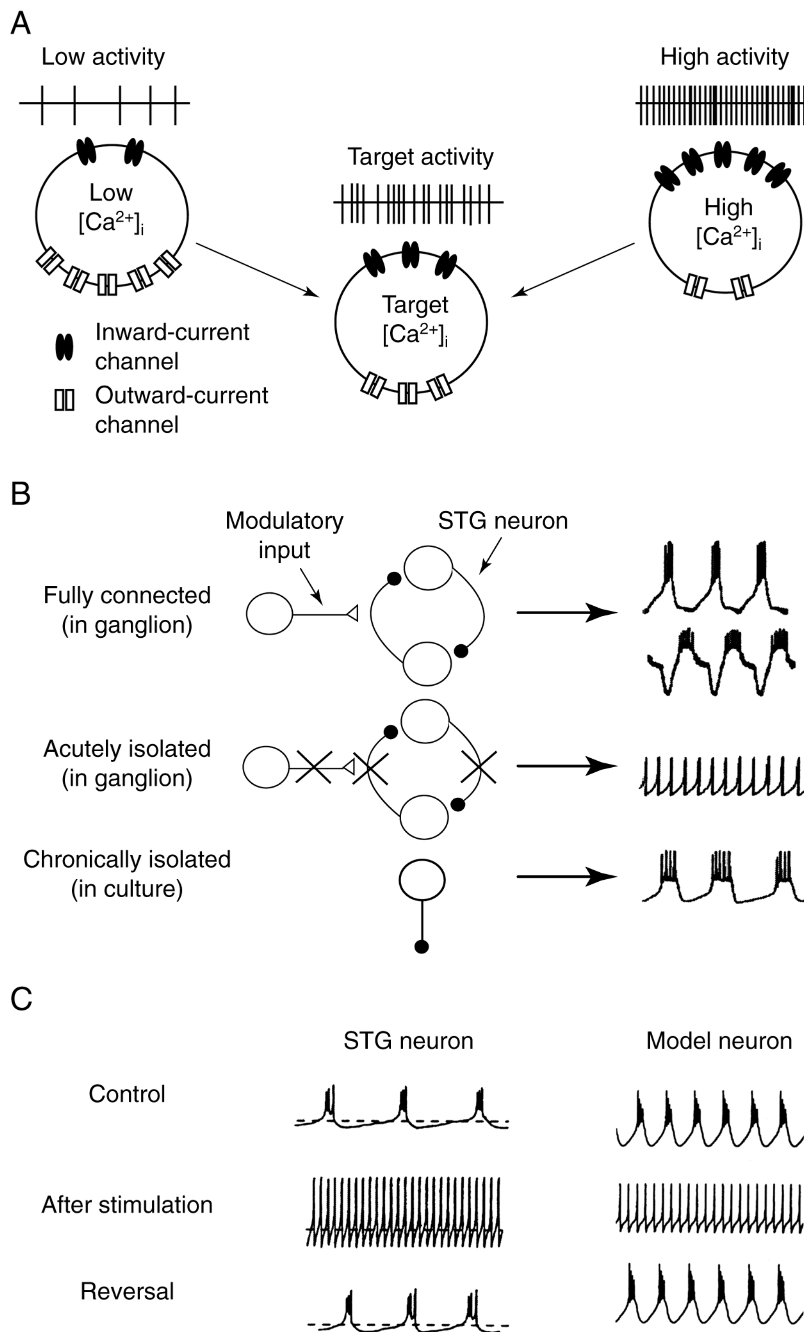

Fig. 1. ***Modification of the balance of inward and outward currents by activity.*** **(A)** *Theoretical and experimental work suggests that intracellular Ca^{2+} concentration {$[Ca^{2+}]_i$} might regulate the balance of inward and outward currents generated by a neuron[14–20]. This balance is regulated to keep $[Ca^{2+}]_i$ within a particular target range. During periods of low activity, when the firing rate falls, $[Ca^{2+}]_i$ falls below the target range. This leads to a compensatory increase in inward current and decrease in outward current, which enhances the excitability of the neuron, raises firing rates and brings $[Ca^{2+}]_i$ back within the target range (central diagram). Conversely, if activity is too high and $[Ca^{2+}]_i$ exceeds the target range, inward currents decrease and outward currents increase. This decreases the excitability of the neuron and again brings $[Ca^{2+}]_i$ back within the target range (central diagram). For more complex neurons that have the ability to fire Ca^{2+}-dependent bursts of action potentials, shifting the balance of conductances to favor inward currents will promote bursting, while shifting the balance to favor outward currents will promote tonic firing[15]. The effects of isolation on the intrinsic firing properties of stomatogastric ganglion (STG) neurons are shown in* **(B)**. *When fully connected, STG neurons fire in bursts owing to reciprocal inhibitory connections with pacemaker neurons and modulatory input from other ganglia. When acutely isolated from synaptic and modulatory inputs, the majority of STG neurons fire tonically. During chronic isolation, however, they gain the ability to generate bursts intrinsically, without the need for external drive, due to an increase in inward current and a decrease in outward current.* **(C)** *Excitatory drive can reverse the acquisition of intrinsic bursting in isolated neurons. When isolated STG neurons are stimulated for several hours in a pattern that mimics their normal rhythmic drive, they undergo a transition from bursting (Control) back to tonic firing (After stimulation). When the drive is terminated, they slowly regain the ability to fire in bursts (Reversal). A model neuron [based on the principle described in* (A)*] can mimic the effects of external drive on the intrinsic properties of STG neurons.* (C) reproduced, with permission, from Refs 15,17.

Neurons grow, change shape, lose and gain synapses, and there is a constant turnover of the ion channels that determine the neuron's electrical-firing properties. Yet despite this constant flux, neurons are able to maintain relatively constant firing properties over time. Much theoretical and experimental work suggests that neurons accomplish this by regulating the balance of ionic conductances they express homeostatically as a function of ongoing activity[14–19]. The model that has emerged is that the balance of a neuron's inward and outward conductances is regulated by a signal, such as the intracellular Ca^{2+} concentration, that is well correlated with activity. For example, when the firing rate of a neuron is low, the intracellular Ca^{2+} concentration falls and conductances are modified to increase firing and raise intracellular Ca^{2+} levels. Conversely, when activity is high, intracellular Ca^{2+} levels rise, and conductances are modified to decrease activity (Fig. 1A).

An experimental test of these ideas has come from work on the stomatogastric ganglion (STG) of decapod crustaceans. *In situ*, STG neurons fire in bursts as a consequence of both intrinsic conductances and synaptic and modulatory inputs from other neurons. When acutely isolated from these synaptic and modulatory influences, the majority of STG neurons fire tonically, but when chronically isolated in culture they gain the ability to fire in bursts (Fig. 1B). This change in intrinsic firing properties is due to a coordinated increase in inward conductance and decrease in outward conductance[16]. Several hours of rhythmic drive, which approximates the neuron's normal pattern of synaptic inputs, reverses this transition through a mechanism that is mediated by a rise in intracellular Ca^{2+} levels (Fig. 1C)[15]. This suggests that the rhythmic drive normally received *in situ* suppresses intrinsic bursting by raising intracellular Ca^{2+} levels, which modifies the balance of ionic conductances.

A similar process occurs in intact STG neurons, where rhythmic activity resumes several days after chronic isolation from descending modulatory inputs[18,19]. It is not clear, however, whether this change in intrinsic properties in the intact ganglion is activity dependent, because inducing slow activity during the period of isolation, by application of a muscarinic agonist, does not prevent it[18]. This modulator-induced activity might have been too slow to prevent the transition to intrinsic bursting. Alternatively, the ability to transform intrinsically bursting neurons into tonically firing neurons through intracellular stimulation (Fig. 1C)[15], and the slower spontaneous acquisition of bursting properties that follows isolation from modulatory inputs[18,19], might occur by different but complementary mechanisms.

While the former occurs though activity-dependent changes in intracellular Ca^{2+} levels[15], the latter could depend, for example, on the removal of a modulator that normally has a trophic role in the suppression of intrinsic bursting[18].

The ability of ongoing activity to modify the firing properties of STG neurons[15,20] suggests that these properties will depend on the temporal (and perhaps spatial[21]) patterns of synaptic input. For example, the same total amount of synaptic current will have different effects on intrinsic excitability depending on whether it is patterned in a way that results in high intracellular Ca^{2+} levels or low intracellular Ca^{2+} levels, and this will, in turn, depend on the intrinsic firing properties of a particular neuron[14]. Work on the activity-dependent regulation of crayfish motoneuron terminals illustrates this point well: many of the essential morphological and physiological features that distinguish tonically firing motoneurons from phasically firing motoneurons appear to arise from the pattern of activity that these neurons encounter during development[22–24].

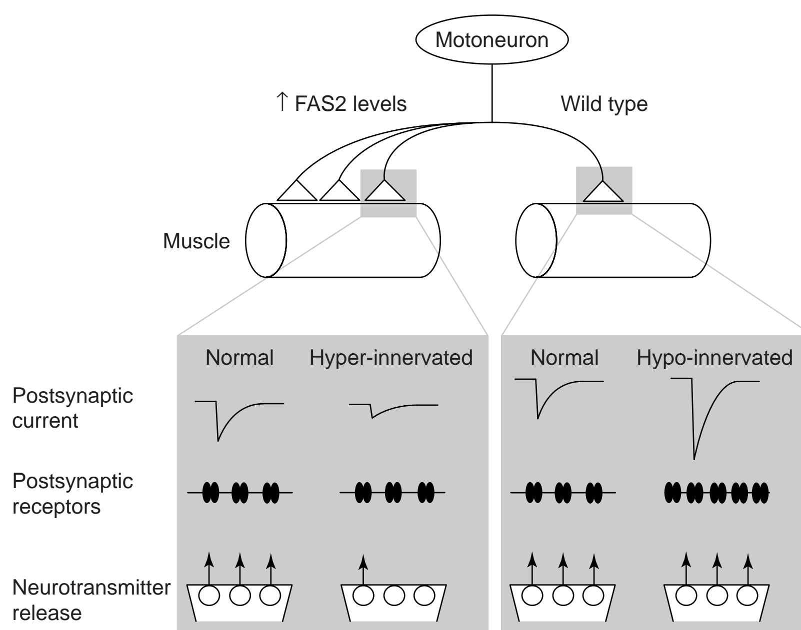

Fig. 2. ***Regulation of synaptic efficacy at the*** **Drosophila** ***neuromuscular junction.*** *Selective overproduction of the cell-adhesion molecule fasciclin II (FAS2) in one of two targets of a motoneuron causes a redistribution of synaptic terminals between the two targets, so that the FAS2-enriched muscle is hyper-innervated and the wild-type muscle is hypo-innervated[29]. At the hyper-innervated fiber, the probability of presynaptic neurotransmitter release at each terminal is decreased. The average size of the postsynaptic current generated by each terminal is, therefore, smaller and the total current generated by all the terminals together is similar to a normally innervated fiber. At the hypo-innervated fiber, neurotransmitter release probability is unaffected, but the current generated by release of single quanta of neurotransmitter increases. This could be due to an increase in postsynaptic receptors, as shown, or to a change in the amount of neurotransmitter packaged into each vesicle.*

Synaptic homeostasis at the *Drosophila* NMJ

At the *Drosophila* NMJ, there is a very restricted range of synaptic efficacies over which the muscle will function properly. Many muscle fibers are innervated by a single motoneuron and, if the strength of that connection is too high or too low, the muscle will either experience tetanus or will fail to contract. Recent work suggests that the strength of neuromuscular transmission in *Drosophila* is regulated precisely to preserve synaptic efficacy within a functional range. Genetic manipulations have made it possible to perturb different parameters of synaptic transmission and then determine the nature of the compensatory response. These studies have revealed a complex set of interlocking mechanisms that operate both presynaptically and postsynaptically to preserve synaptic efficacy[25].

The degree of motoneuron innervation of *Drosophila* muscle fibers can be regulated by overproduction or under-production of a cell-adhesion molecule called fasciclin II (FAS2)[26–30]. When FAS2 synthesis is decreased to approximately 10% of the levels in the wild-type flies, the number of synaptic contacts (boutons) between the motoneuron and muscle fiber decrease. Yet, remarkably, muscle excitation in this mutant is normal. This is due to a compensatory increase in the number of active zones in each bouton, which acts to preserve the total number of synaptic vesicles released upon activation of the motoneuron and, thus, produces excitatory postsynaptic currents of normal amplitude[28].

The complexity of this regulatory process is revealed by manipulations that selectively increase FAS2 levels in one of two targets innervated by the same motoneuron (Fig. 2)[29,30]. The muscle fiber with increased FAS2 levels becomes hyper-innervated by the motoneuron, while the fiber with normal FAS2 levels is hypo-innervated. This seems to occur through a redistribution of the same number of motoneuron terminals between the two targets, as the total number of boutons formed by the motoneuron is the same as for wild-type flies. This synaptic redistribution activates compensatory processes that normalize muscle excitation, but the mechanism differs for increased and decreased innervation. At the terminals with increased innervation of the muscle, there is a decrease in the probability of neurotransmitter release but quantal amplitude is normal. In contrast, at the terminals with decreased innervation of the muscle, there is an increase in quantal amplitude that compensates for the reduction in neurotransmitter release[29].

The evidence for the role of neuronal activity in synaptic homeostasis at the *Drosophila* NMJ is somewhat indirect. Decreasing the levels of glutamate receptors or producing a constitutively active form of protein kinase A, both decrease the quantal amplitude at the NMJ, and are thus likely to reduce muscle depolarization. These manipulations trigger an increase in neurotransmitter release probability similar to that found in hypo-innervated muscles[31]. Interestingly, a similar process has been found in vertebrate neuromuscular transmission, where a reduction in the number of functional postsynaptic ACh receptors results in increased presynaptic release[32–34].

Multiplicative scaling of cortical synaptic strengths

Maintaining activity within functional boundaries is a more difficult problem for neurons in the CNS than for muscles. These neurons receive thousands of synaptic inputs that can be excitatory, inhibitory or modulatory, and the neuron must usually integrate many inputs to cross the firing threshold. In addition, during learning and development, all of these inputs might be changing simultaneously in both number and strength. What are the rules for regulating synaptic strengths that allow central neurons in the CNS to balance the effects of all of these changes as the

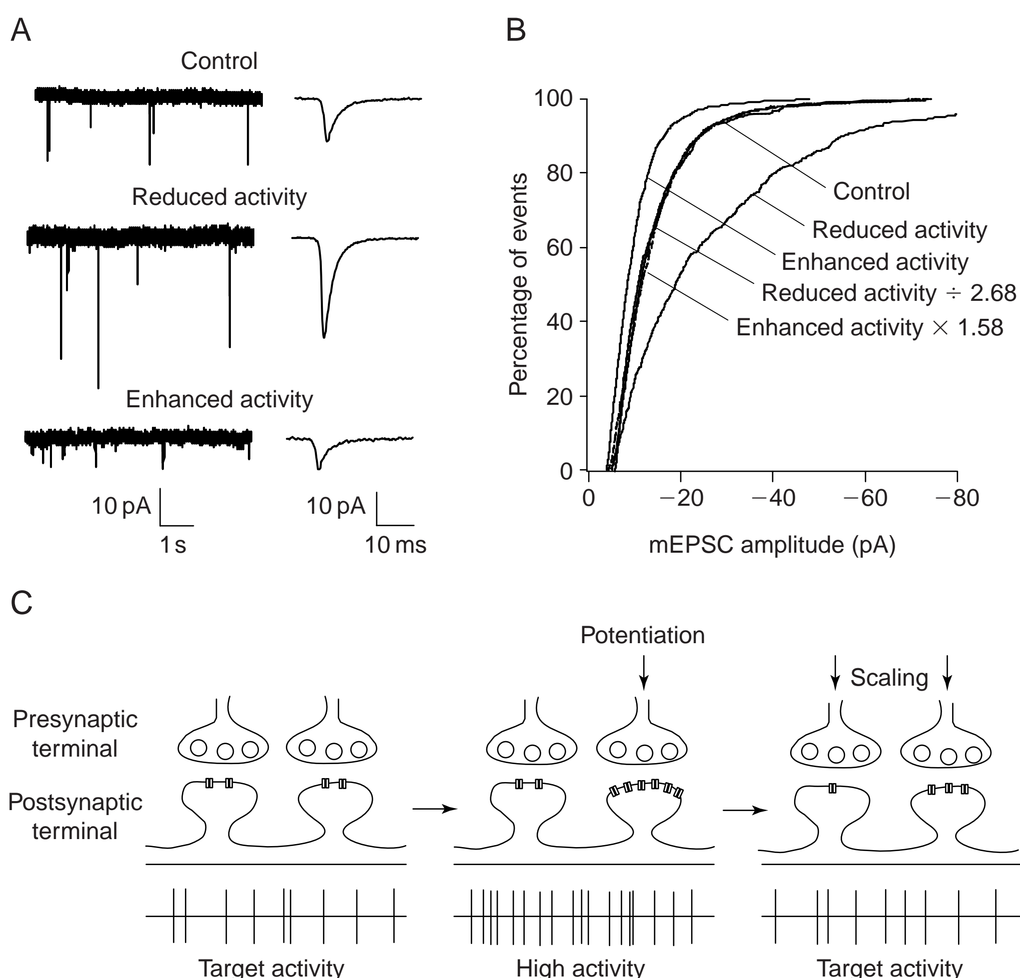

Fig. 3. ***Multiplicative scaling of synaptic strengths in cortical pyramidal neurons.*** **(A)** *The amplitude of miniature excitatory postsynaptic currents (mEPSCs) depends on the history of activity of the neuron[35]. Spontaneous activity was increased or blocked for 48 h in cortical cultures and mEPSCs were recorded from voltage-clamped pyramidal neurons. Raw data from neurons grown for 48 h under control conditions, with activity blocked or with activity enhanced are shown on the left. On the right, the average mEPSC for neurons grown under each condition is shown. Respectively, activity-blocked neurons and activity-enhanced neurons have larger and smaller mEPSCs than control neurons.* **(B)** *mEPSC amplitudes plotted as cumulative histograms. The entire activity-blocked distribution is shifted towards larger amplitudes, while the activity-enhanced distribution is shifted towards smaller amplitudes. Both the activity-blocked and activity-enhanced distributions can be almost perfectly transformed into the control distributions by dividing each amplitude by 2.68 (activity blocked) or by multiplying each amplitude by 1.58 (activity enhanced). This suggests that synaptic strengths can be scaled by activity by multiplying (or dividing) each synaptic strength by the same factor.* **(C)** *A model of multiplicative scaling, which suggests how scaling might interact with synapse-specific changes in synaptic strength such as LTP. Two synapses initially have equal strength (left). When one is potentiated (center), the firing rate of the postsynaptic neuron rises. This causes a proportional decrease in the strength of both synapses through the removal of AMPA receptors. The firing rate of the neuron falls again but the difference between the two synapses is preserved (right). Note that the potentiation could be either presynaptic or postsynaptic in origin.* (A) *and* (B) reproduced, with permission, from Ref. 35.

network develops over time? The answer that is beginning to emerge is that cortical and hippocampal neurons regulate their own firing rates by scaling the strength of their synaptic inputs up or down as a function of activity[35–38].

In cultured cortical neurons, the strength of excitatory synaptic connections between pyramidal neurons can be scaled up or down globally as a function of firing rate (Fig. 3A). When firing rates increase, excitatory synaptic strengths are scaled down, and when firing rates decrease, excitatory synaptic strengths are scaled up[35]. This occurs through increases or decreases in the quantal amplitude of the AMPA receptor-mediated component of excitatory neurotransmission, which mediates the bulk of excitatory transmission between neurons in the CNS. This change in quantal amplitude appears to occur at all of the synapses in a neuron, probably as a result of changes in postsynaptic AMPA-receptor number[35,38]. This 'synaptic scaling' differs in a number of important ways from Hebbian, synapse-specific forms of synaptic plasticity such as LTP (Ref. 5) and long-term depression LTD (Ref. 6.) First, it appears to be independent of NMDA-receptor activation. Second, it is somewhat slow, requiring hours or days of altered activity to modify synaptic strengths. This is probably important for allowing neurons to integrate average activity over a long time scale, without their responding to moment-to-moment fluctuations in firing rates. Finally, this form of plasticity occurs through the scaling of all synaptic strengths up or down by the same multiplicative factor (Fig. 3B)[35]. This multiplicative scaling of synaptic strengths has the right characteristics to preserve relative differences between inputs (such as those produced by LTP or LTD), while allowing a neuron to adjust the total amount of synaptic excitation it receives (Fig. 3C).

An interesting aspect of synaptic scaling is that it can promote competition between synaptic inputs to a particular neuron. Activity-dependent competition for the formation and stabilization of inputs is thought to have an important role in the fine-tuning of synaptic connections during development[3,7,8]. One way that competition can occur is if strengthening of some inputs leads to weakening of others. Several forms of heterosynaptic depression, where potentiation of one set of inputs depresses other inputs to the same neuron or muscle fiber, have been described[39,40]. Interestingly, synaptic scaling can also promote competition, because if some inputs are strengthened and the postsynaptic firing rate begins to rise, all of the neuron's inputs will be scaled down in strength. If synaptic weakening is the prelude to elimination, as has been suggested[40–43], then synaptic scaling could allow a neuron to shed its weakest inputs in response to the strengthening of others.

Neurotrophins and homeostasis in cortical networks

An important aspect of synaptic scaling in cultured cortical networks is that the direction of change of a synapse depends on both the nature of the synapse and the nature of the postsynaptic neuron[35–37]. Cortical pyramidal neurons are embedded in complex networks with extensive recurrent excitatory and

inhibitory feedback. Pyramidal-neuron firing rates reflect not only excitatory drive, but also the balance between excitatory inputs from other pyramidal neurons and inhibitory inputs from GABAergic interneurons. Activity in the interneurons is, in turn, driven by excitation from the pyramidal neurons (Fig. 4A). This suggests that to increase pyramidal-neuron firing rates, excitatory input to pyramidal neurons should be increased but excitatory input to interneurons should not. Conversely, to reduce pyramidal-neuron firing rates excitatory input to pyramidal neurons should decrease but excitatory input to interneurons should increase.

Such differential regulation of different classes of cortical synapses requires a signal that is well correlated with activity and that can act simultaneously at many sites in the network. The neurotrophin, brain-derived neurotrophic factor (BDNF), fits this description: it is produced by cortical pyramidal neurons and its high-affinity receptor, trkB, is present on both pyramidal and interneurons[44–47]. Production of BDNF (Refs 48–51), and probably release[52,53], is regulated by activity, and BDNF is thought to have a number of important roles in the activity-dependent development of cortical circuits[54]. Recent work demonstrates that synaptic scaling in cultured cortical networks is mediated through the activity-dependent release of BDNF. In pyramidal neurons, BDNF prevents the increase in quantal amplitude produced by activity blockade, whereas blocking the action of endogenous BDNF mimics the effects of activity blockade[37]. These data strongly suggest that a reduction in release of BDNF is the signal that scales pyramidal-neuron synapses up in response to reduced activity.

Interestingly, BDNF has opposite effects on the excitatory synapses on pyramidal neurons and interneurons[37]. Whereas BDNF reduces pyramidal-neuron synaptic strengths, it increases interneuronal synaptic strengths. As a consequence, manipulations that decrease BDNF levels (and, thus, signal reduced pyramidal-neuron activity) reconfigure these cultured cortical networks to recruit more excitation onto pyramidal neurons (Fig. 4B), and manipulations that increase BDNF levels (and, thus, signal increased pyramidal-neuron activity) act to recruit more inhibitory input to pyramidal neurons (Fig. 4C). These data suggest that an important function for this neurotrophin is to promote stability in pyramidal-neuron firing rates by regulating the strength of synaptic connections at many sites within the network.

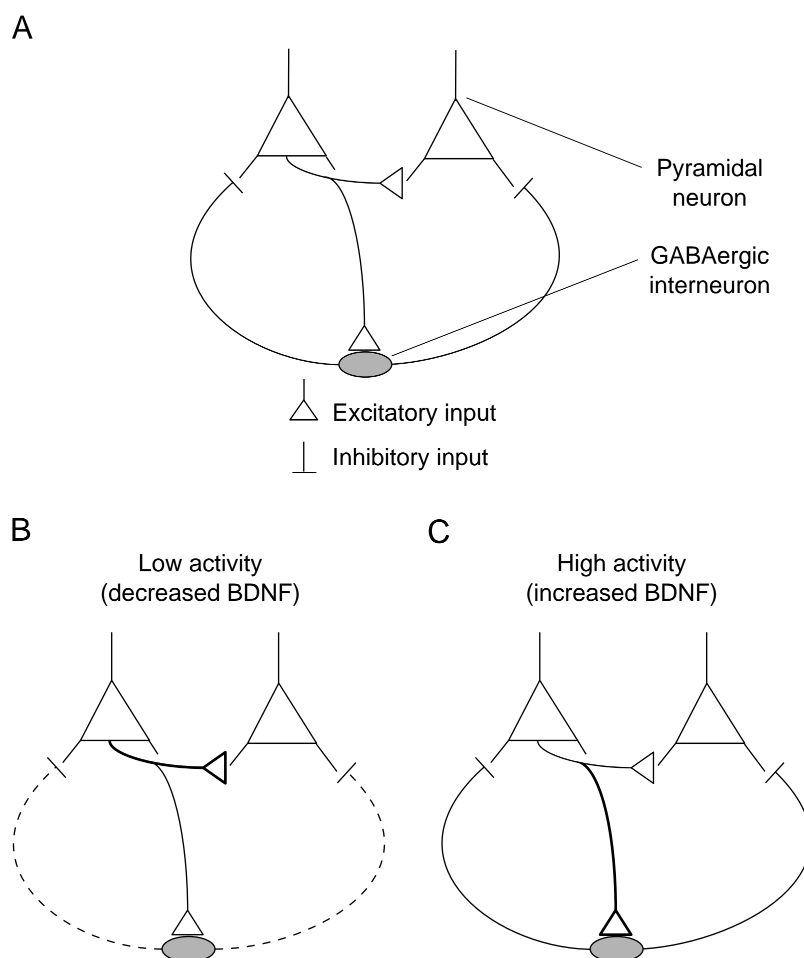

Fig. 4. ***Homeostatic regulation of pyramidal-neuron firing rates by the activity-dependent release of brain-derived neurotrophic factor (BDNF).*** **(A)** *Schematic of a cortical circuit showing recurrent excitatory and inhibitory connections between excitatory pyramidal neurons and inhibitory GABAergic interneurons.* **(B)** *When pyramidal neuron firing rates fall, BDNF release from pyramidal neurons decreases. This causes excitatory connections between pyramidal neurons to increase in strength[37] (thick line), and reduces inhibition from the interneurons[36](broken line). These effects combine to increase the net excitatory drive to pyramidal neurons, and to raise pyramidal neuron firing rates.* **(C)** *When activity rises, BDNF release increases. This strengthens excitatory connections from pyramidal neurons onto interneurons (thick line), thus increasing the feedback inhibition onto pyramidal neurons and lowering pyramidal neuron firing rates. High activity also decreases the strength of excitatory connections between pyramidal neurons, but this effect is not mediated by BDNF, but by some other unidentified factor[37].*

Activity-dependent stabilization of synaptic connections

Synaptogenesis is a complex process requiring that neurons extend their axons long distances and form selective contacts with their targets. Once contacts are made, a process of activity-dependent refinement occurs, in which appropriate connections are strengthened and stabilized, and inappropriate connections are lost[3,8,55]. This process is similar in many respects to Hebbian mechanisms of synaptic plasticity, in that stabilization requires correlated pre- and postsynaptic activity, is dependent on Ca^{2+} influx through NMDA receptors, and is likely to involve activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)[55]. But the processes of synapse formation and elimination have an additional requirement. During synaptogenesis, axons and dendrites undergo a process of dynamic extension and retraction that allows many pre- and postsynaptic elements to come into contact with each other to form 'trial' synapses. This growth and retraction must be regulated by activity at the synapse, so that strengthening of the synapse halts growth and stabilizes the pre- and postsynaptic structures, while weakening of the synapse allows the pre- and postsynaptic elements to continue to grow and contact other more-desirable partners.

Recent work on the *Xenopus* retinotectal system suggests that activity, operating through activation of CaMKII, controls both the physiological and the morphological maturation of tectal synapses[56–58]. Immature retinal axons contact a number of postsynaptic tectal targets and, when stimulated, activate NMDA- but not AMPA-receptor-mediated currents, probably because the immature synapses contain NMDA receptors but not AMPA receptors. As the synapses mature and become more spatially restricted, AMPA-receptor mediated currents appear and the retinal axons become

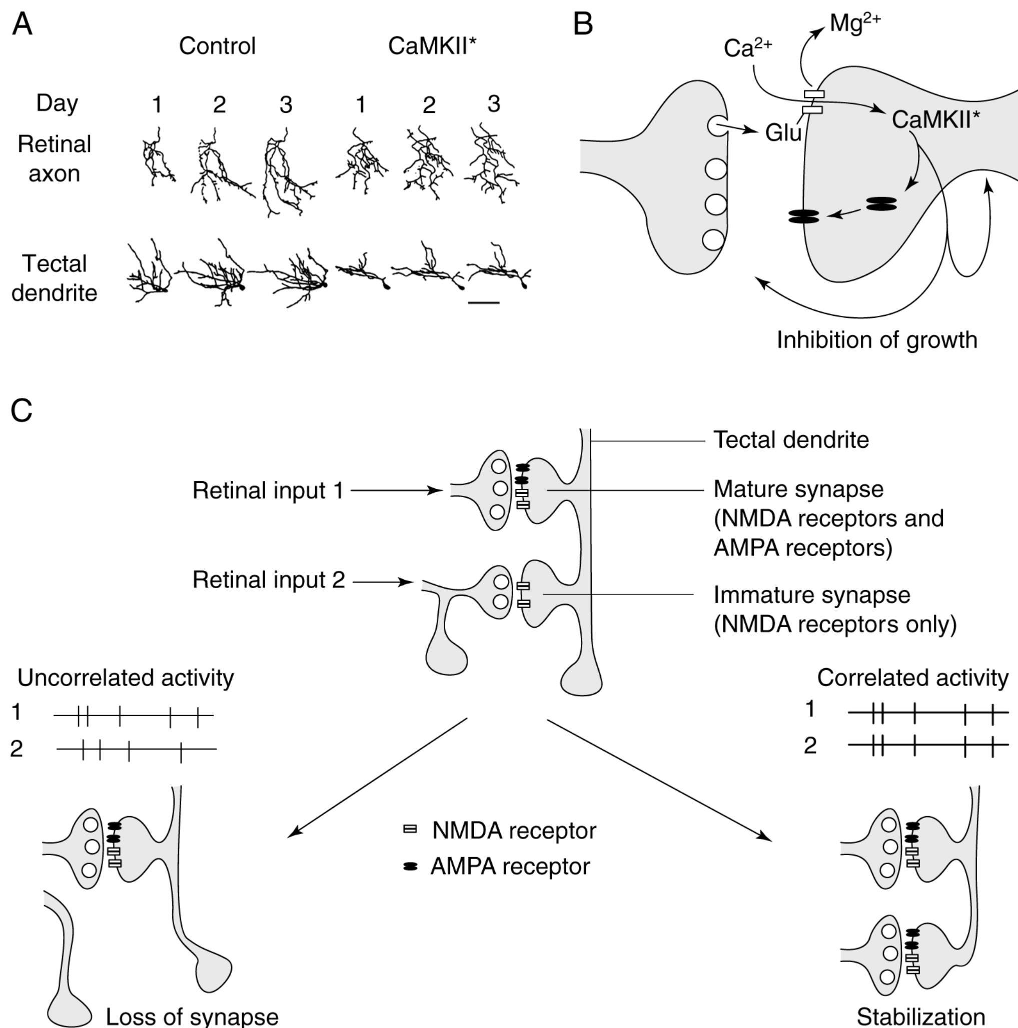

Fig. 5. ***Regulation of process outgrowth and synapse stabilization in the* Xenopus *retinotectal system by postsynaptic* Ca^{2+}*/calmodulin-dependent protein kinase (CaMKII) activity.*** **(A)** *When a constitutively active form of CaMKII (CaMKII*) is produced selectively in* Xenopus *tectal neurons, there is a reduction in the outgrowth of retinal axons that innervate the tectal neurons. Representative axonal arbors from control and CaMKII*-treated animals over a three-day growth period are shown. This CaMKII* also inhibits dendritic growth in the tectal neurons: representative dendritic arbors from control and CaMKII* animals over a three-day growth period are shown. Scale bar, 25 μm.* **(B)** *Schematic of the role of CaMKII in synaptic maturation. When presynaptic activity coincides with postsynaptic depolarization, the* Mg^{2+} *block of NMDA receptors is lifted and* Ca^{2+} *enters the postsynaptic terminal, activating CaMKII. This CaMKII* then initiates both the insertion of AMPA receptors into the presynaptic membrane and the stabilization of pre- and postsynaptic structures, by inhibiting growth and retraction. Abbreviation: Glu, glutamate.* **(C)** *In order to achieve simultaneous presynaptic activity and postsynaptic depolarization at an immature synapse, which does not have AMPA receptors, the activity at this synapse must be correlated with that of a nearby mature synapse. By activating CaMKII in the postsynaptic terminal, correlated activity will inhibit retraction and outgrowth of nearby axonal and dendritic branches, and stabilize the immature synapse. In contrast, activity that is not correlated will not inhibit retraction of axonal and dendritic branches. The immature synapse will be lost and outgrowth will continue.* (A) repoduced, with permission, from Refs 57,58.

capable of depolarizing the tectal neurons[55,56]. Recent work suggests the following model for this process: when the activity of immature inputs is correlated with mature inputs that successfully depolarize the postsynaptic neuron, the voltage-dependent block of the NMDA receptor is lifted and Ca^{2+} enters the immature postsynaptic terminal. This activates CaMKII, which leads to the insertion of AMPA receptors into the presynaptic membrane (Fig. 5)[55,56].

But how does activity produce the simultaneous morphological stabilization of the synapse? This process also appears to be controlled by postsynaptic activation of CaMKII. Selective postsynaptic expression of the gene encoding a constitutively active form of CaMKII slows the outgrowth of the axonal arbors of retinal neurons and decreases their complexity[57]. This constitutively active form of CaMKII also stabilizes the arbor structure of the postsynaptic tectal dendrites[58]. This suggests that when immature inputs are correlated with mature inputs, local synaptic activation of CaMKII will coordinately stabilize presynaptic and postsynaptic structures, and induce the development of functional synaptic transmission. Conversely, if activity in the tectal input is not correlated with postsynaptic activity and CaMKII activity at the trial synapse is low, extension and retraction of pre- and postsynaptic structures will continue and new synapses can be formed. An interesting prediction of this work is that the total number of synapses formed by presynaptic and postsynaptic elements will be limited by activity. As the number of inputs increases and postsynaptic activity rises, synaptogenesis will be inhibited because both axonal and dendritic outgrowth will slow. The reverse of this scenario is that when activity falls, synaptogenesis will be promoted once again.

Emerging themes in homeostatic plasticity

Investigations into the role of homeostatic plasticity in network function are relatively new, but several themes from a diverse set of systems are beginning to emerge. First, neurons can use their own activity as a feedback signal to modify intrinsic excitability and to maintain total synaptic strength at a roughly constant level. Several distinct mechanisms exist that can adjust synaptic efficacy, which include changes in neurotransmitter release probability at the *Drosophila* NMJ, and changes in quantal amplitude at the *Drosophila* NMJ and at synapses in the CNS. Second, at the *Drosophila* NMJ, changes in synapse number produce compensatory changes in strength while at tectal synapses, changes in strength produce compensatory changes in outgrowth (which should influence synapse number). This suggests that these two variables are intimately and inversely related during circuit formation. Finally, neurotrophins are likely to have a key role in the homeostatic regulation of cortical synaptic strengths. The advantage of such a mechanism in complex neuronal networks is that trophic factors can act at a number of sites in the network to produce a well-orchestrated response to changes in activity. By stabilizing synapse number and strength and promoting competition between inputs, homeostatic plasticity is likely to

emerge as an important partner to Hebbian plasticity that allows networks to satisfy the joint requirements for change and stability.

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