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Too Many Cooks? Intrinsic and Synaptic Homeostatic Mechanisms in Cortical Circuit Refinement

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Abstract

Maintaining the proper balance between excitation and inhibition is critical for the normal function of cortical circuits. This balance is thought to be maintained by an array of homeostatic mechanisms that regulate neuronal and circuit excitability, including mechanisms that target excitatory and inhibitory synapses, and mechanisms that target intrinsic neuronal excitability. In this review, I discuss where and when these mechanisms are used in complex microcircuits, what is currently known about the signaling pathways that underlie them, and how these different ways of achieving network stability cooperate and/or compete. An important challenge for the field of homeostatic plasticity is to assemble our understanding of these individual mechanisms into a coherent view of how microcircuit stability is maintained during experience-dependent circuit refinement.

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INTRODUCTION

Epilepsy is a disorder of circuit excitability that affects 1%–2% of the population, often to devastating effect. What is extraordinary about this incidence to a neuroscientist who studies cortical microcircuits is not that it is so high, but rather that most people, most of the time, are not epileptic. This observation is surprising because many of the circuits within our cerebral cortex are composed of highly unstable networks with extensive positive feedback (Burkhalter 2008), where even small changes in the balance between excitation and inhibition can set off uncontrolled seizure-like activity. Yet despite the existence of many forces that continuously perturb the balance between excitation and inhibition, such as learning-related or developmental changes in synapse number and strength, somehow, most of the time, our brains manage to compensate for these changes and maintain stable function. Our brains appear to be constructed so that the flexibility that enables us to adapt and learn is balanced by stabilizing mechanisms that preserve overall network function, and these forces

of plasticity and stability are able to coexist and cooperate without interfering with each other.

How do our brains achieve this remarkable feat? In the past two decades, major inroads have been made into elucidating the mechanisms that allow neurons and circuits to maintain stable function in the face of these ongoing perturbations. Our brains employ an array of classic homeostatic negative feedback mechanisms that allow neurons and/or circuits to sense how active they are and to adjust their excitability to keep this activity within some target range (Davis 2006, Marder & Goaillard 2006, Turrigiano & Nelson 2004), and collectively these stabilizing mechanisms have been termed homeostatic plasticity. To implement homeostatic plasticity neurons need to sense some aspect of “activity,” and when this measure deviates from a target value, a force must be generated that adjusts excitability to move neuronal activity back toward this target. In principle, if individual neurons can stabilize their own firing, then overall network activity will also be stabilized; however, depending on network architecture, the rules for homeostatic regulation are likely to be tuned for the function of particular neurons within the circuit. For example, one might predict that excitatory and inhibitory neurons would use distinct homeostatic rules. Although much has been learned about the cellular and synaptic mechanisms of homeostatic plasticity in reduced preparations such as neuronal cultures, little is currently known about how homeostatic plasticity is implemented in complex, highly recurrent microcircuits such as those of the neocortex, where many different cell types subserve distinct functions and likely express unique forms of plasticity.

Neuronal firing arises from the interplay between synaptic currents and the intrinsic firing properties of a neuron. Thus one can imagine two fundamentally different ways that neurons could homeostatically regulate excitability (**Figure 1**). First, they could slowly adjust synaptic strengths up or down in the right direction to stabilize average neuronal firing rates (Turrigiano et al. 1998). Conversely, instead of regulating synaptic strengths, they

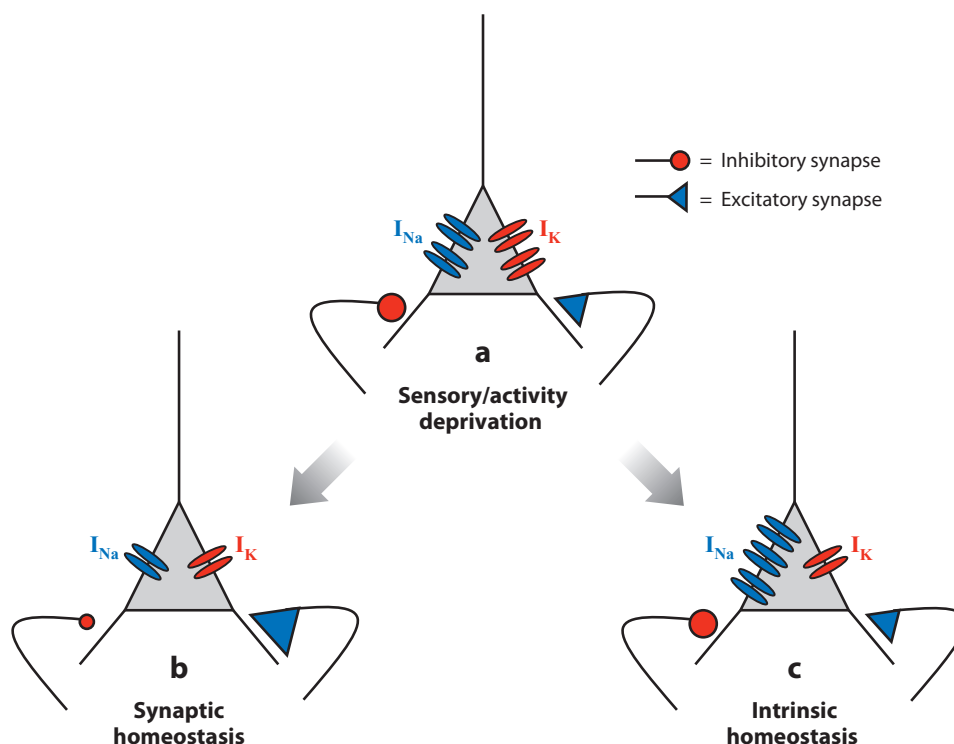


Figure 1

Two fundamentally different mechanisms for the homeostatic regulation of neuronal firing. (a) Neuronal activity is determined both by the strength of excitatory and inhibitory synaptic inputs and by the balance of inward and outward voltage-dependent conductances that regulate intrinsic excitability, here illustrated as the relative number of Na (blue) and K (red) channels. Neurons can compensate for reduced sensory drive either by using synaptic mechanisms to modify the balance between excitatory and inhibitory inputs (b) or by using intrinsic mechanisms to modify the balance of inward and outward voltage-dependent currents (c).

could modulate intrinsic excitability to shift the relationship between synaptic input and firing rate (their “input-output curve”) (Desai et al. 1999, Turrigiano et al. 1994). In principle, both of these processes could work, and many neurons appear able to undergo homeostatic regulation of firing via either mechanism (Desai et al. 1999, Maffei & Turrigiano 2008b, Turrigiano et al. 1998). This raises the questions of why neurons sometimes use one method and sometimes another, whether important functional differences exist between these two forms of homeostatic plasticity, and whether there are hierarchical rules for their engagement. In this review, I focus on recent work examining the interactions between intrinsic and synaptic homeostasis,

using cortical networks as a major example. I begin by reviewing the evidence for these two forms of homeostatic regulation, explore what is currently known about their interaction in both reduced preparations and in vivo, and speculate about their function. Understanding the rules that underlie network homeostasis is likely to shed important light onto disease processes to which imbalances in excitation and inhibition contribute, such as epilepsy, schizophrenia, and autism.

HOMEOSTATIC REGULATION OF NEURONAL FIRING

Compelling evidence from a variety of systems, both in vivo and in vitro, indicates that

circuit activity is homeostatically regulated to maintain firing rates and/or firing patterns within certain functional boundaries. An early example came from studies of invertebrate central pattern generators (CPGs), where investigators observed that perturbations that made these networks arrhythmic resulted in compensatory changes in intrinsic neuronal properties that, over time, restored rhythmicity (Haedo & Golowasch 2006; Thoby-Brisson & Simmers 1998; Turrigiano et al. 1994, 1995); Gonzalez-Islas & Wenner (2006) found a similar phenomenon in developing vertebrate spinal cord central pattern generators. Similarly, central neurons in dissociated cultures are able to maintain average firing rates around a homeostatic set point. When cortical or hippocampal neurons are induced to fire more than normal, over many hours, firing returns to baseline levels, and if neuronal firing is reduced over time neurons also compensate and again firing is restored to baseline (Burrone et al. 2002, Turrigiano et al. 1998). These studies lend strong support to the idea that neuronal circuits possess mechanisms that maintain firing around a homeostatic stable point. Because fluctuations in firing are the currency of information transfer in the brain, it may seem at first glance to be highly problematic for neurons to maintain stable average firing rates without impairing information flow. Most forms of homeostatic compensation in central neurons are slow and operate over hours to days, many orders of magnitude slower than the moment-to-moment fluctuations in firing that transmit information (Turrigiano & Nelson 2004). Thus the temporal characteristics of firing rate homeostasis appear designed to prevent interference with the business of information transfer.

In contrast with the strong evidence for firing rate (or firing pattern) homeostasis cited above, for many *in vivo* vertebrate circuits the evidence is less direct. In both visual tectum and visual cortex, studies have shown that neuronal response amplitudes remain roughly constant following visual deprivation, suggesting that homeostatic compensation has occurred (Chandrasekaran et al. 2007, Mrsic-Flogel et al.

2007). Furthermore, lowering sensory drive in both visual and auditory cortex can generate compensatory changes in synaptic and/or intrinsic network properties that enhance circuit excitability when measured *ex vivo* (Maffei et al. 2004, 2006; Maffei & Turrigiano 2008b; Vale & Sanes 2002), but it is not yet clear whether these changes result in true homeostasis, that is, act to maintain an activity set point.

Further complicating matters, in both sensory cortex and hippocampus the mechanisms and sites of homeostatic compensation are strongly developmentally regulated (Desai et al. 2002, Echejoen et al. 2007). Research has demonstrated this point most clearly in the primary visual cortex, where studies in rodent have shown that compensation for lowered visual drive is implemented in a layer- and cell-type-specific manner. In layer 4 (the primary cortical input layer), homeostatic compensation is present early in development but turns off at the opening of the classical visual system critical period (CP) (Desai et al. 2002; Maffei et al. 2004, 2006). In contrast, in the upper cortical layers (which mediate extensive lateral interactions between functionally related cortical regions), compensation is absent early, turns on at the onset of the CP, and remains active into adulthood (Goel & Lee 2007, Maffei & Turrigiano 2008b). Thus not all neurons, nor indeed all local microcircuits, are subject to homeostatic regulation at all times in an animal's life. A major challenge for the field is to identify the rules that guide the placement and timing of homeostatic mechanisms within complex neural circuits.

SYNAPTIC HOMEOSTASIS

Central neurons are embedded in complex networks composed of many distinct cell types, including both excitatory neurons and a rich variety of inhibitory neurons with distinct morphologies and functions. In most networks, small changes in the balance between excitation and inhibition (the E/I balance) can have a major impact on ongoing activity, and compelling evidence indicates that the E/I balance

is tightly regulated (Atallah & Scanziani 2009, Pouille et al. 2009, Shu et al. 2003). Given this complexity, the ability of networks to compensate for external or internal perturbations and to maintain stable firing is not trivial and likely requires mechanisms that can adjust both excitatory and inhibitory synaptic strengths in a cell-type-specific manner. Indeed, experimenters have now uncovered a rich variety of homeostatic synaptic mechanisms that operate on both excitatory and inhibitory synapses, which I describe below in turn.

Synaptic Scaling of Excitatory Synapses

Investigators have identified several forms of homeostatic plasticity of excitatory synapses. For example, there is evidence for both “global” mechanisms such as synaptic scaling that operate on all a neuron’s synapses and “local” mechanisms that act on individual or small groups of synapses (Turrigiano 2008, Yu & Goda 2009). Similarly, some forms of synaptic homeostasis occur through presynaptic and others through postsynaptic changes in function (Davis & Bezprozvanny 2001). Currently, the best studied form of homeostatic plasticity at central excitatory synapses is global synaptic scaling, which I will focus on here both because of space limitations and because of strong evidence that this form of homeostatic plasticity is important for the in vivo function of cortical networks; several recent reviews provide an excellent discussion of presynaptic and/or local forms of compensatory synaptic plasticity (Thiagarajan et al. 2007, Turrigiano 2008, Yu & Goda 2009).

Synaptic scaling was first identified in cultured neocortical neurons, where investigators observed that pharmacological manipulations of activity induced compensatory and bidirectional changes in the unit strength of glutamatergic synapses (Turrigiano et al. 1998). By measuring miniature excitatory postsynaptic currents (minis) mediated by 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) and N-methyl D-

aspartate-type glutamate receptors, researchers found that modulating network activity induced uniform increases or decreases in the entire mini amplitude distribution, in effect scaling postsynaptic strength up or down (Desai et al. 2002, Gainey et al. 2009, Turrigiano et al. 1998). These changes in mini amplitude translate into changes in the amplitude of evoked transmission, with little or no change in short-term synaptic dynamics (Maffei et al. 2004, Watt et al. 2000, Wierenga et al. 2005). Such a postsynaptic scaling process is predicted to stabilize activity without changing the relative strength of synaptic inputs, thus avoiding disrupting information-storage mechanisms that rely on differences in synaptic weights. Synaptic scaling has now been demonstrated in a variety of central neurons both in vitro and in vivo, including neocortical and hippocampal pyramidal neurons and spinal neurons (Desai et al. 2002, Goel & Lee 2007, Kim & Tsien 2008, Knogler et al. 2010; O’Brien et al. 1998, Stellwagen & Malenka 2006, Turrigiano et al. 1998). A fascinating and still unanswered question is the nature of the biophysical mechanism that allows neurons to scale synaptic strengths up and down proportionally.

How do neurons sense perturbations in activity during synaptic scaling? Two recent studies have provided strong evidence that synaptic scaling is a cell-autonomous process in which neurons sense changes in their own activity through changes in firing/depolarization and calcium influx. For example, selectively blocking firing in an individual cortical pyramidal neuron scales up that neuron’s synaptic strengths to the same degree as does blockade of network activity through a process that requires a drop in somatic calcium influx, reduced activation of calcium/calmodulin dependent (CaM) Kinase Kinase (CaMKK) and CaM Kinase IV (CaMKIV), and transcription (Ibata et al. 2008). This signaling pathway then leads to enhanced accumulation of AMPA-type glutamate receptors (AMPA) in the postsynaptic membrane at all excitatory synapses, thus scaling up mini amplitude and enhancing evoked transmission. This global enhancement

of AMPAR abundance in response to activity blockade requires sequences on the C-terminus of the GluR2 subunit of the AMPAR (Gainey et al. 2009), which distinguishes synaptic scaling from other forms of synaptic enhancement such as long-term potentiation (LTP) that require sequences on the GluR1 subunit (Malenka & Bear 2004). Thus synaptic scaling up is fundamentally different from LTP: It operates over a longer temporal scale (hours) and a wider spatial scale (global) and utilizes trafficking steps that target the GluR2 subunit to enhance AMPAR abundance at synapses.

Like scaling up in neocortical neurons, scaling down in hippocampal slice cultures in response to enhanced activity (using channel-rhodopsin and optical stimulation) can also be induced by cell-autonomous changes in calcium influx, and this process also involves CaMKK/CaMKIV signaling and transcription and requires the GluR2 subunit for its expression (Goold & Nicoll, 2010). Unlike CaMKK, CaMKIV was found to be necessary but not sufficient to trigger a reduction in synaptic strength, suggesting that CaMKK activates several parallel signaling pathways that cooperate to reduce synaptic strength. In hippocampal neurons, driving individual neurons to fire induces synapse loss as well as reduced quantal amplitude (Goold & Nicoll, 2010), something not seen in young neocortical or spinal neurons in response to elevated network activity (O'Brien et al. 1998, Turrigiano et al. 1998); it is not clear whether this discrepancy is due to differences in activation method, neuron type, or neuron age between studies.

We do not currently understand the entire sequence of events that lead from cell-autonomous changes in calcium influx to bidirectional changes in AMPAR abundance, and a number of parallel signaling pathways, and dozens of molecules, likely contribute to synaptic scaling. For example, there is evidence that the neurotrophin brain-derived neurotrophic factor (BDNF) (Rutherford et al. 1998), the immediate early gene *Arc* (Shepherd et al. 2006), the cytokine $\text{TNF}\alpha$ (Steinmetz & Turrigiano, Stellwagen & Malenka 2006),

the immune molecule MHC1 (Goddard et al. 2007), Beta3 integrins (Cingolani et al. 2008), and the polo-like kinase 2 (Plk2)-CDK5 signaling pathway (Seeburg et al. 2008), among others, are all involved in or essential for synaptic scaling. Several of these molecules are known to regulate AMPA receptor trafficking; for example, *Arc* interacts with the endocytic machinery that removes AMPAR from the membrane (Chowdhury et al. 2006), $\text{TNF}\alpha$ directly increases synaptic AMPAR accumulation (Beattie et al. 2002; Stellwagen et al. 2005), and Beta3 integrins regulate AMPAR surface expression (Cingolani et al. 2008). Some of these molecules are involved in only one branch of synaptic scaling (either scaling up or scaling down), indicating that although some signaling elements (such as CaMKK and CaMKIV) are shared during bidirectional scaling (Goold & Nicoll, 2010, Ibata et al. 2008), others are not (Rutherford et al. 1998, Shepherd et al. 2006, Stellwagen et al. 2005). Many of these signaling molecules are likely to play permissive rather than instructive roles in synaptic scaling, as has recently been shown for $\text{TNF}\alpha$ (Steinmetz & Turrigiano, 2010).

Synapse-Type Specificity of Excitatory Synaptic Scaling

Neural circuits are composed of many excitatory and inhibitory cell types interconnected in highly specific ways, and it would clearly be counterproductive from a homeostatic point of view to scale all synapses up or down together without regard for the function of the post-synaptic neuron, and indeed there is evidence that the rules for scaling excitatory synapses are cell-type specific. In cultured cortical and hippocampal neurons, excitatory synapses onto pyramidal neurons are scaled up by activity blockade, whereas excitatory synapses onto γ -Aminobutyric acid (GABA)-ergic interneurons are either unaffected (Rutherford et al. 1998) or reduced (Chang et al., 2010), possibly depending on GABAergic cell type. Conversely, enhancing network activity increases excitatory transmission onto GABAergic interneurons

(Chang et al. 2010, Rutherford et al. 1998) through a process that involves the activity-dependent regulation of the immediate early gene *Narp*. *Narp* appears to be secreted by presynaptic pyramidal neurons and accumulates preferentially at excitatory synapses into parvalbumin-positive interneurons (Chang et al. 2010), suggesting that homeostatic regulation of excitatory synapses onto these neurons is a noncell-autonomous process that depends on pyramidal neuron activity, a theme I revisit below in the discussion of inhibitory synapse scaling.

Not all excitatory neurons express synaptic scaling at all times during development. As discussed above, in visual cortex the expression of synaptic scaling is strongly developmentally regulated and is expressed by layer 4 pyramidal neurons early in postnatal development, but then turns off in layer 4 and turns on in layer 2/3 pyramidal neurons around the opening of the classical visual system CP (Desai et al. 2002; Goel & Lee 2007; Maffei et al. 2004, 2006; Maffei & Turrigiano 2008b). Similarly, activity blockade in hippocampal networks scales up CA1 but not CA3 excitatory synapses, suggesting that the rules for expression of scaling in hippocampus are cell-type specific (Kim & Tsien 2008). These studies underscore the point that not all cell types or networks are designed to maintain homeostasis of firing at all periods of development. Rather, they suggest that synaptic scaling is specifically expressed when and where it is needed.

An interesting and unanswered question is whether a given postsynaptic neuron can preferentially scale one subtype of excitatory synapse while leaving others unaffected. In cortical neurons in dissociated culture and in vivo, it is thought that all excitatory synapses are affected equally during synaptic scaling in response to a drop in activity, based on the observation that the entire distribution of mini amplitudes is scaled up or down proportionally. However, if a synapse type that represented only a small fraction of a neuron's synapses was not affected, this analysis is unlikely to be sensitive enough to detect the resulting

deviation from pure scaling. Conversely, if synapse-specific and global synaptic plasticity mechanisms (that affect quantal amplitude) are activated simultaneously by a given activity manipulation, then the net change in mini distribution may not follow a simple scaling rule even though synaptic scaling of all excitatory synapses has occurred. Thus the presence of proportional scaling of the quantal amplitude distribution does not rule out some synapse specificity, nor does its absence necessarily rule out that synaptic scaling has occurred. Changes in the mini amplitude distribution induced by manipulations of network activity should thus be interpreted with due caution.

Homeostatic Regulation of Inhibitory Synapses

A powerful way to stabilize network activity is to reciprocally regulate the relative strengths of excitatory and inhibitory synapses, and a long literature shows that inhibition is regulated by long-lasting changes in activity and/or sensory drive. Early work in primate and rodent visual cortex demonstrated that visual deprivation or inhibition of retinal activity with tetrodotoxin (TTX) decreased immunoreactivity for GABA (Benevento et al. 1995; Hendry et al. 1994; Hendry & Jones 1986, 1988) and reduced inhibition and inhibitory synapse number in cortical and hippocampal cultures (Marty et al. 1997, Rutherford et al. 1997), leading to a reduction in the amount of functional inhibition (Rutherford et al. 1997). These studies raised the possibility that inhibitory synaptic strength is regulated homeostatically in the opposite direction from excitatory synapses.

Indeed, the same paradigm that scales up miniature excitatory postsynaptic currents onto pyramidal neurons in culture scales down the amplitude of miniature inhibitory postsynaptic currents through a mechanism that can involve both changes in accumulation of postsynaptic GABAA receptors and a reduction in presynaptic GABAergic markers, such as GAD65 (Hartman et al. 2006, Kilman et al. 2002). Both in vitro and in vivo studies have suggested that homeostatic regulation of

inhibition can occur via a constellation of changes in postsynaptic strength, synapse number, and GABA packaging and release in various combinations (Hartman et al. 2006, Kilman et al. 2002, Maffei et al. 2004); this variability in expression mechanism could reflect several distinct inhibitory plasticity mechanisms (as is the case for homeostasis at excitatory synapses) or perhaps the great diversity of inhibitory synapse types in hippocampus and cortex.

The distinct and opposing plasticity rules at excitatory and inhibitory synapses appear to be designed to stabilize the firing of principal (in cortex, and hippocampus, pyramidal) neurons, suggesting that, from a network point of view, it is the activity of the principal neurons that is homeostatically constrained. This raises the question of whose activity matters in the regulation of inhibition: the presynaptic inhibitory neuron or the postsynaptic pyramidal neuron. This question was recently addressed in hippocampal cultures by preventing firing in either the postsynaptic pyramidal neuron or the presynaptic inhibitory neuron, while measuring inhibitory synapses onto the pyramidal neuron; the answer was that neither manipulation was sufficient to mimic the effects of blocking network firing. This result argues that, in contrast to synaptic scaling of excitatory synapses, homeostatic regulation of inhibition is a noncell-autonomous process that either requires changes in both pre- and postsynaptic activity simultaneously or is triggered by global changes in network activity.

Interneurons come in a wide range of functional varieties, and although in neocortical networks the net effects of changes in excitation and inhibition appear to be homeostatic (Maffei et al. 2004, Rutherford et al. 1998, Turrigiano et al. 1998), different classes of inhibitory synapse are regulated differently by lowered activity. When sensory drive to primary visual cortex is lowered in vivo, connections from fast-spiking basket cells onto layer 4 pyramidal neurons are reduced in amplitude, whereas connections from another class of interneuron become sparser but stronger (Maffei et al. 2004). Similarly, activity

blockade with TTX in neocortical slice cultures differentially regulates different classes of inhibitory synapses (Bartley et al. 2008), whereas in hippocampal networks, activity blockade reduces net inhibition but increases the strength of a specific, endocannabinoid-sensitive class of inhibitory input (Kim & Alger 2010). Under some conditions, net inhibition in hippocampal networks can change in the same direction as excitation (Echegoyen et al. 2007), but whether this acts to enhance or oppose stability is not entirely clear. All these studies strongly support the idea that inhibitory synapses are regulated in a subtype-specific manner, presumably because the molecular machinery that subserves plasticity at inhibitory synapses is different at different synapse types.

Several released factors, including BDNF and endocannabinoids, have been implicated in the homeostatic regulation of inhibition (Kim & Alger 2010, Rutherford et al. 1997, Swanwick et al. 2006). Different subclasses of interneuron have receptors for endocannabinoids and BDNF, suggesting a mechanistic basis for cell-type specificity in the homeostatic regulation of inhibition.

HOMEOSTASIS OF INTRINSIC EXCITABILITY

Changes in intrinsic excitability that alter a neuron's input-output function can strongly affect network behavior, and there is mounting evidence for activity-dependent plasticity of intrinsic excitability in a variety of neurons (Marder & Goaillard 2006, Zhang & Linden 2003). Just as synaptic plasticity comes in several flavors and can be induced through a variety of signaling cascades, intrinsic plasticity also exhibits great diversity and can be either destabilizing or homeostatic. For example, the classic stimuli used to induce hippocampal synaptic plasticity also induce intrinsic plasticity, and these changes can either boost the effects of synaptic plasticity through local changes in dendritic excitability or serve a homeostatic function by regulating somatic spike generation (Fan et al. 2005, Frick et al. 2004, Narayanan

et al. 2010). Similarly, both destabilizing and homeostatic forms of intrinsic plasticity have now been well-documented in neocortical neurons (Breton & Stuart 2009, Cudmore et al. 2010, Cudmore & Turrigiano 2004, Desai et al. 1999, Nataraj et al. 2010); furthermore, as for synaptic homeostatic mechanisms, there appear to be a variety of intrinsic plasticity processes that operate over distinct spatial and temporal scales to modulate neuronal activity (Daoudal & Debanne 2003, Zhang & Linden 2003). A fascinating and largely unanswered question is whether homeostatic forms of intrinsic and synaptic plasticity serve redundant or distinct functions within neuronal networks.

Many organisms live for decades, whereas the ion channels that subserve neuronal excitability turn over on a timescale of days to weeks. How, then, do neurons maintain stability in their intrinsic firing characteristics? An idea that has emerged over the past two decades is that neurons regulate their intrinsic excitability in a homeostatic manner by using some signal (such as intracellular calcium) to trigger changes in the balance of inward and outward currents (Marder & Goaillard 2006). This process has been beautifully documented in invertebrate central pattern generators, and both theoretical and experimental work has lent considerable support to the idea that these neurons can compensate intrinsically for changes in modulatory drive and so maintain their ability to fire in bursts (Golowasch et al. 1999, LeMasson et al. 1993, Marder & Prinz 2002, Turrigiano et al. 1994). In vertebrate neurons, the regulation of neuronal input/output curves serves as a gain-control mechanism underlying adaptive plasticity of the vestibulo-ocular reflex (Gittis & du Lac 2006, Nelson et al. 2005) and contributes to the activity-dependent development of the *Xenopus* retinotectal system (Aizenman et al. 2003, Pratt & Aizenman 2007). In cultured neocortical pyramidal neurons, the same activity-deprivation paradigm that leads to scaling up of synaptic strengths also enhances intrinsic excitability so that neurons fire more to the same synaptic input (Desai et al. 1999). As for invertebrate neurons, this process occurs

through the reciprocal regulation of inward and outward voltage-dependent currents (generally with no change in passive electrical properties), although the exact currents targeted by intrinsic plasticity depend on the identity and function of the targeted neuron (Breton & Stuart 2009, Desai et al. 1999, Nelson et al. 2005). It was recently shown that in addition to changes in inward and outward current densities, enhanced firing (by changes to calcium influx) can regulate the location of the axon initial segment (AIS) so that it moves further from the soma (Grubb & Burrone 2010). Conversely, auditory deprivation can increase the length of the AIS in auditory brain stem neurons (Kuba et al. 2010), suggesting that modifications in the location and size of the AIS may be a bidirectional and fairly general neuronal response to changes in activity. The exact contribution of these changes in AIS to neuronal excitability has not been determined, but they are predicted to alter firing threshold and so could play an important role in the homeostatic regulation of neuronal excitability.

Although the phenomenon of homeostatic intrinsic plasticity has now been widely documented, very little is known about the underlying induction and expression mechanisms. The cell biological processes that regulate the abundance and trafficking of glutamate and other neurotransmitter receptors are likely to apply to voltage-gated ion channels as well, but it remains unclear whether the same signaling pathways target voltage- and ligand-gated channels in parallel during homeostatic plasticity or whether synaptic and intrinsic plasticity are triggered by distinct signaling pathways. Understanding the mechanisms of intrinsic plasticity will be key for illuminating whether synaptic and intrinsic plasticity cooperate or compete during experience-dependent plasticity.

INTERPLAY BETWEEN SYNAPTIC AND INTRINSIC PLASTICITY: WHAT TO USE WHEN?

The discussion above highlights the intriguing point that neural circuits have a variety of

homeostatic mechanisms to choose from: When faced with a destabilizing perturbation, they could respond by regulating inhibition, excitation, intrinsic excitability, or all the above. This raises the perplexing questions of why neurons should possess both synaptic and intrinsic homeostatic mechanisms, whether these two forms of homeostasis are simply redundant or subserve distinct functions, and whether they are generally induced in parallel or whether there is some kind of hierarchy that regulates when and where they are brought into play. Some insights into these questions are being generated by recent studies into the cellular mechanisms of experience-dependent plasticity within visual cortex.

Visual cortex has been used extensively as a model system for exploring the role of experience in refining cortical function, and much work has gone into determining the cellular plasticity mechanisms that underlie various phases of cortical circuit refinement, using a venerable sensory deprivation paradigm pioneered by Hubel and Wiesel decades ago (Hubel & Wiesel 1970, Wiesel & Hubel 1963). Although visual cortical plasticity was initially largely ascribed to Hebbian forms of synaptic plasticity, it has recently become clear that sensory deprivation (like activity deprivation *in vitro*) engages a rich array of plasticity mechanisms, including the entire cast of homeostatic characters identified above (Feldman 2009, Nelson & Turrigiano 2008). Moreover, these mechanisms are employed in a cell-type-specific, layer-specific, and developmentally regulated manner, making for a degree of complexity that can seem bewildering. For example, in rodents, the functional effects of visual deprivation and the underlying plasticity mechanisms are different during the pre-CP just after eye opening and during the classical visual system CP that begins a week later (Maffei & Turrigiano 2008a); I discuss the role of synaptic and intrinsic homeostatic plasticity during both developmental periods in turn below.

During the pre-CP, visual deprivation induces compensatory changes in local circuit excitability in layer 4 by scaling up excitatory

synapses onto pyramidal neurons and reducing inhibition (Desai et al. 2002, Maffei et al. 2004). However, these synaptic changes are not accompanied by changes in intrinsic excitability, indicating that in layer 4 during the pre-CP synaptic changes are used preferentially to compensate for reduced sensory drive. This finding is in marked contrast with experiments on young visual cortical neurons in culture, where activity deprivation (using TTX) induces compensatory changes in synaptic strengths and intrinsic excitability in parallel (Desai 2003). This raises the possibility that in neocortical circuits synaptic homeostatic mechanisms might be used first, and intrinsic mechanisms might be engaged only when synaptic mechanisms do not suffice—for example, when firing is blocked in culture using TTX so that neurons cannot restore firing no matter how strongly they regulate synaptic strengths (Desai et al. 1999).

The functional effects of visual deprivation change abruptly at the beginning of the classical visual system CP and so do the expression patterns of various forms of plasticity within the microcircuits of V1. In rodents, the response to visual deprivation during the CP follows a biphasic time course: There is an initial loss of responsiveness to the deprived eye, followed more slowly (over several days) by a gain of responsiveness to both eyes. The net effect of these two processes is to shift the relative drive to the two eyes to favor the open eye [and so to shift ocular dominance (OD)] (Frenkel & Bear 2004, Kaneko et al. 2008, Mrsic-Flogel et al. 2007). The potentiation phase also occurs in monocular cortex or in response to binocular deprivation in the binocular cortex, indicating that it does not require competition between the two eyes and raising the possibility that it is induced by a homeostatic rather than a Hebbian mechanism (Kaneko et al. 2008, Mrsic-Flogel et al. 2007).

Manipulations that block synaptic scaling *in vitro* (namely, blocking $\text{TNF}\alpha$ or Arc signaling) also block the delayed potentiation during visual deprivation, raising the possibility that synaptic scaling underlies response potentiation during the CP (Kaneko et al.

2008, McCurry et al. 2010). However, there is currently little direct evidence for this hypothesis, and these manipulations likely interfere with other plasticity mechanisms as well as synaptic scaling. Furthermore, although synaptic scaling has not been examined in binocular cortex, in monocular cortex, lid suture (the method of deprivation generally used to induce OD plasticity) does not scale up mEPSC amplitude in layer 2/3 pyramidal neurons, although retinal blockade and dark-rearing do (Desai et al. 2002, Goel & Lee 2007, Maffei & Turrigiano 2008b). Instead, lid suture triggers an enhancement of intrinsic excitability (Maffei & Turrigiano 2008b), raising the possibility that intrinsic homeostatic plasticity rather than synaptic scaling might underlie delayed response potentiation. Resolving this issue will require further experiments in binocular cortex to examine the time course and induction requirements of these two forms of homeostatic plasticity. Why homeostatic compensation in layer 2/3 is delayed in response to lid suture is unclear. Also unanswered is why retinal activity block and lid suture induce different forms of homeostatic plasticity within layer 2/3. One possibility is that lid suture decorrelates sensory drive to cortex more than does blocking retinal activity (Linden et al. 2009), and this decorrelation drives very strong synaptic depression in layer 2/3 (Maffei & Turrigiano 2008b, Rittenhouse et al. 1999). It may be that this depression exceeds the ability of synaptic scaling to compensate, which then triggers intrinsic homeostatic plasticity. In this view, there is a hierarchy between synaptic scaling and intrinsic plasticity, with intrinsic plasticity coming into play only when synaptic mechanisms cannot fully compensate for perturbations in drive.

In hippocampal networks, activity deprivation can also activate both intrinsic and synaptic homeostasis, but the hierarchical relationship between them appears to be different from that suggested above by work in neocortex. In hippocampal slice cultures, for example, synaptic and intrinsic mechanisms are also dissociable, but intrinsic mechanisms seem to come into play first before synaptic

mechanisms kick in (Karmarkar & Buonomano 2006). Furthermore, activity blockade in vivo was observed to induce hyperexcitability in the CA1 region, which was accompanied by both synaptic and intrinsic changes in young, but only intrinsic changes in old, CA1 pyramidal neurons (Echegoyen et al. 2007). These studies demonstrate that in hippocampus, as in neocortex, a complex and developmentally regulated interplay occurs between these two forms of homeostatic plasticity. In contrast to visual cortex and hippocampus, the retinotectal system in *Xenopus* seems to use intrinsic mechanisms preferentially for homeostatic compensation. Reducing synaptic drive leads to enhanced intrinsic excitability, but not vice versa: When neuronal excitability is suppressed by overexpressing a K^+ channel, neurons respond by upregulating Na^+ currents to bring intrinsic excitability back up (Pratt & Aizenman 2007). Thus the rules by which intrinsic and synaptic mechanisms are applied to achieve homeostatic compensation seem to vary across systems according to rules we have not yet fathomed.

CONCLUDING REMARKS

Neural circuits utilize a complex mix of synaptic and intrinsic mechanisms to optimize their function and/or adapt to a changing environment (Feldman 2009, Nelson & Turrigiano 2008). These include an array of homeostatic mechanisms that allow circuits to regulate differentially the strength of excitation, inhibition, and intrinsic excitability. Functionally, intrinsic and synaptic plasticity well may not have identical effects on information transfer. Synaptic scaling adjusts the gain of the input, rather than the gain of the output, and does so in a manner that can reciprocally change excitation and inhibition, thus modifying the E/I balance. In contrast, intrinsic excitability modifies the contribution of a neuron to circuit function without changing synaptic currents, but the functional effects of this modulation will depend on how excitability is modified. For example, if intrinsic plasticity affects the slope of the

neuronal input-output function without affecting threshold, then the neuron becomes more or less sensitive to both excitation and inhibition, and this form of gain control will not involve changes in the effective E/I ratio. In contrast, if excitability is regulated by sliding the input-output function left or right to modify the firing threshold, then the relative effectiveness of excitation and inhibition will

be modified by intrinsic plasticity; moving the threshold left makes excitation more effective at firing the neuron and inhibition less able to prevent firing, and vice versa. One great challenge currently facing the field of cortical plasticity is to elucidate how the appropriate homeostatic mechanism is selected by particular firing patterns or activity levels to achieve the appropriate outcome for the circuit.

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