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Invited review

# Tuning into diversity of homeostatic synaptic plasticity

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ABSTRACT

Neurons are endowed with the remarkable ability to integrate activity levels over time and tune their excitability such that action potential firing is maintained within a computationally optimal range. These feedback mechanisms, collectively referred to as "homeostatic plasticity", enable neurons to respond and adapt to prolonged alterations in neuronal activity by regulating several determinants of cellular excitability. Perhaps the best-characterized of these homeostatic responses involves the regulation of excitatory glutamatergic transmission. This homeostatic synaptic plasticity (HSP) operates bidirectionally, thus providing a means for neurons to tune cellular excitability in response to either elevations or reductions in net activity. The last decade has seen rapid growth in interest and efforts to understand the mechanistic underpinnings of HSP in part because of the theoretical stabilization that HSP confers to neural network function. Since the initial reports describing HSP in central neurons, innovations in experimental approaches have permitted the mechanistic dissection of this cellular adaptive response and, as a result, key advances have been made in our understanding of the cellular and molecular basis of HSP. Here, we review recent evidence that outline the presence of distinct forms of HSP at excitatory glutamatergic synapses which operate at different sub-cellular levels. We further present theoretical considerations on the potential computational roles afforded by local, synapse-specific homeostatic regulation.

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## 1. Introduction

Defined patterns of pre- and post-synaptic activity can induce input-specific changes in synaptic strength. The two most studied of these activity-dependent synaptic plasticity processes are long-term potentiation (LTP) and long-term depression (LTD). These processes exhibit many of the features described in a model postulated by Donald Hebb more than 50 years ago to account for the ability of a neuronal network to store information (Hebb, 1949). As a result, tremendous efforts have been devoted to define the cellular and molecular mechanisms of LTP and LTD, and to understand their role as substrates of learning and memory (Kerchner and Nicoll, 2008; Kessels and Malinow, 2009; Lisman and Raghavachari, 2006; Lisman, 2009; Malenka and Nicoll, 1999; Malinow and Malenka, 2002; Whitlock et al., 2006). However, the simple implementation of Hebbian-type LTP and LTD processes in different neuronal network models soon revealed an inherent stability problem for network function (Lazar et al., 2009; Miller and MacKay, 1994; Turrigiano and Nelson, 2004).

Destructive instabilities of both synapse and network function are readily apparent in exclusively Hebbian neural network models (Lazar et al., 2009; Miller and MacKay, 1994; Shouval et al., 2002; Turrigiano and Nelson, 2004). Specifically, these models demonstrate that the positive-feedback nature of Hebbian plasticity favors unconstrained synaptic potentiation and depression, thus leading to synapses which hit their functional 'ceiling' (for instance, by reaching maximum AMPA receptor number and density), or synapses that are driven toward functional demise by depressive mechanisms. An important consequence of such positive-feedback behavior in neural circuits is runaway excitation and epileptogenic neural activity (Lazar et al., 2009; Turrigiano and Nelson, 2004). During early childhood, the brain experiences intense growth and development and these normal processes have been linked to enhanced susceptibility to seizure in young children (Wong, 2005). However, the overall risk of pediatric seizure remains relatively low

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considering the breadth of developmental changes at play, prompting some to hypothesize that homeostatic mechanisms exist to stabilize neural networks during development (Davis, 2006; Turrigiano and Nelson, 2004) and during mature brain function (Lazar et al., 2009; Sullivan and de Sa, 2006, 2008; Toyoizumi et al., 2005; Turrigiano, 2012, 2008; Watt and Desai, 2010; Yeung et al., 2004), but see (de Vries and van Slochteren, 2008; Gilson and Fukai, 2011; Houweling et al., 2005; Thivierge and Cisek, 2008).

Several distinct homeostatic plasticity mechanisms have been described, each in principle providing neurons the means to tune and maintain overall levels of spiking activity within biologically-determined set points. Neurons accomplish this by actively regulating several determinants of cellular excitability, including intrinsic excitability (Grubb and Burrone, 2010; Turrigiano, 2011) and synaptic strength (Turrigiano, 2012; Turrigiano et al., 1998; Turrigiano and Nelson, 2004). In particular, the discovery of homeostatic synaptic plasticity (HSP) has received considerable interest because it provides a theoretically plausible solution to the instability problem of Hebbian networks described above. With features that closely resemble the well described denervation supersensitivity at the neuromuscular junction (Cannon, 1949), homeostatic synaptic plasticity (HSP) is characterized by the bidirectional regulation of synaptic strength in response to prolonged alterations in network activity (O'Brien et al., 1998; Turrigiano, 2008; Turrigiano et al., 1998).

Borrowing from the widely-used distinction between the induction and expression of Hebbian forms of synaptic plasticity (LTP/LTD), one can conceptualize a loosely analogous distinction between the *induction* and *expression* of HSP. Determining key mechanistic features of both these processes, in addition of determining how they interact with classic Hebbian synaptic plasticity, is necessary for developing a thorough understanding of the role played by HSP in neuronal computation. Here, we review recent studies that reveal fundamental mechanistic insights in the *induction* (*eg.*, cell-autonomous vs. non-cell-autonomous) and *expression* (cell-wide vs. local) of HSP and consider conceptual refinements for the role of local forms of HSP in stabilizing neuronal information storage and processing at excitatory glutamatergic synapses.

## 2. The locus of homeostasis

Whereas Hebbian LTP and LTD occurs within seconds to minutes in response to relatively short bouts of synaptic stimulation, the presence of HSP is experimentally revealed when neuronal activity is altered over longer periods of time (*i.e.*, hours to days). For instance, in perhaps its simplest and most intuitively tractable form, HSP is revealed when neuronal network activity is globally suppressed for a prolonged period of time (*eg.*, by applying tetrodotoxin, TTX, to the culture media for many hours; see Fig. 1B). In response, neurons exhibit a compensatory increase in cellular excitability, in part through a cell-wide upregulation of synaptic AMPAR function (Turrigiano et al., 1998). This slow-acting regulation of excitability is also bidirectional: when neuronal activity is enhanced for many days (*eg.*, by pharmacological network disinhibition), neurons adapt by a cell-wide down-regulation of synaptic AMPAR function.

These core features of homeostatic plasticity entail a number of conceptual postulates: 1) Neurons are endowed with mechanisms that monitor, and integrate over time, some parameters of neuronal activity; 2) These 'sensing' mechanisms are coupled to cellular 'effectors' that operate within a feedback loop to tune neuronal excitability in a direction that is homeostatic in nature (*eg.*, upregulation of excitatory glutamate receptors following prolonged suppression of neuronal activity); 3) whereas HSP's activity sensing and integrating mechanisms are likely continuously operating 'on line', the feedback loop acts over a relatively long time course (*i.e.*, usually requiring several hours for expression). This conceptual framework has helped to guide the mechanistic dissection and understanding of HSP in the last several years (Lee, 2012a; Turrigiano, 2011, 2008).

One feature of HSP that has received particular attention is its "multiplicative" nature. This refers to the observation that during some forms of HSP, the entire amplitude distribution of synaptic strength scales up (or down) by a single common factor, hence the term 'scaling', often used to denominate HSP (Kim et al., 2012; Turrigiano, 1999, 2008; Turrigiano et al., 1998). A common interpretation of the multiplicativity of HSP is that the relative strengths between synapses are maintained during the cell-wide homeostatic scaling process. As such, multiplicative HSP provides a means to tune neuronal excitability without disrupting the previously encoded catalog of Hebbian synaptic engrams. A parsimonious cellular model to account for multiplicativity in HSP posits that a cell-wide mechanism drives the upregulation of AMPAR content across all synapses, with each synapse capturing (or stabilizing) AMPARs in a manner that is proportional to its original strength. However, since global/network-wide pharmacological manipulations (*eg.*, TTX treatment) alter the activity of each neuron within the network, a number of mechanistic details of HSP are left largely intractable. For instance, it is impossible to determine the trigger for HSP induction since two broadly distinct changes take place. First, all neurons in the network are deprived of their ability to generate action potentials. Second, all synapses are deprived of presynaptic input. As such, where is the locus of homeostasis? Do neurons monitor and integrate activity over time by counting action potentials? Or rather, do individual synapses monitor and integrate activity over time by tallying presynaptic inputs? Recent studies have provided interesting insight into this important facet of HSP.

## 3. Cell-autonomous HSP

In a first-step to distinguish between these possibilities, a key series of studies examined the ability of individual neurons to autonomously exhibit HSP (cell-autonomous HSP) by specifically modulating the firing activity of a single neuron embedded within an otherwise normal neural network (i.e., receiving normal ongoing synaptic input; see Fig. 1C) (Burrone et al., 2002; Goold and Nicoll, 2010; Ibata et al., 2008). Borrowing from a previous study at the neuromuscular junction (Paradis et al., 2001), Burrone et al. (2002) developed a single-cell silencing strategy by overexpressing an inwardly rectifying potassium channel, Kir2.1, in a small subset of dissociated hippocampal neurons in culture. Single-cell silencing induced a homeostatic upregulation of glutamatergic transmission as evidenced by a robust enhancement of the frequency of AMPAR-mediated miniature excitatory postsynaptic currents (mEPSCs) in transfected neurons. It was concluded that the reduction of action potential firing by Kir2.1 overexpression induced a homeostatic increase in synaptic function, and thus demonstrated that individual neurons can autonomously express HSP. However, it was later argued that because the Kir2.1-mediated silencing strategy used by Burrone et al. (2002) caused cell-wide hyperpolarization, it was not possible to discriminate the involvement of local dendritic excitability from that of somatic action potentials in triggering HSP. Thus, to specifically ascertain the role of somatic spiking activity in HSP induction, Ibata et al. (2008) used prolonged local perfusion of TTX over the soma of individual neurons. The authors found that suppression of action potential firing for 4 h was sufficient to induce a significant increase in mEPSC amplitude and accumulation of synaptic EYFP-tagged GluA2-