Mechanisms of Homeostatic Synaptic Plasticity in vivo

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Synapses undergo rapid activity-dependent plasticity to store information, which when left uncompensated can lead to destabilization of neural function. It has been well documented that homeostatic changes, which operate at a slower time scale, are required to maintain stability of neural networks. While there are many mechanisms that can endow homeostatic control, sliding threshold and synaptic scaling are unique in that they operate by providing homeostatic control of synaptic strength. The former mechanism operates by adjusting the threshold for synaptic plasticity, while the latter mechanism directly alters the gain of synapses. Both modes of homeostatic synaptic plasticity have been studied across various preparations from reduced in vitro systems, such as neuronal cultures, to in vivo intact circuitry. While most of the cellular and molecular mechanisms of homeostatic synaptic plasticity have been worked out using reduced preparations, there are unique challenges present in intact circuitry in vivo, which deserve further consideration. For example, in an intact circuit, neurons receive distinct set of inputs across their dendritic tree which carry unique information. Homeostatic synaptic plasticity in vivo needs to operate without compromising processing of these distinct set of inputs to preserve information processing while maintaining network stability. In this mini review, we will summarize unique features of in vivo homeostatic synaptic plasticity, and discuss how sliding threshold and synaptic scaling may act across different activity regimes to provide homeostasis.

Keywords: sliding threshold, metaplasticity, BCM theory, synaptic scaling, cortical plasticity, homeostasis, hebbian plasticity

INTRODUCTION

A major challenge faced by neural circuits is to maintain proper neural processing while enabling effective information storage mediated by activity-dependent synaptic plasticity. This is not trivial, because plasticity of synaptic connections alters the flow of information between neurons. Furthermore, activity-dependent synaptic plasticity creates positive feedback, which, when uncompensated, can lead to network instability. In this mini review, we will compare two models of homeostatic synaptic plasticity, sliding threshold and synaptic scaling (Figure 1), and present emerging ideas as to how these two different models may interact to provide network stability (Figure 2).

Earlier studies on neural networks encountered difficulty in maintaining network function when solely engaging Hebbian synaptic plasticity for learning algorithms (discussed in Cooper and Bear, 2012). In one successful theory that allowed network stability, developed by Leon Cooper’s group, the threshold for synaptic plasticity is controlled by integrated past neuronal activity.
scales up excitatory synapses (O'Brien et al., 1998; Turrigiano et al., 1998).

In contrast, synaptic scaling can occur without neural activity. Indeed, blocking all activity with tetrodotoxin (TTX) scales up excitatory synapses, while increasing neural activity by pharmacologically blocking inhibition scales down the strength of synapses (O'Brien et al., 2007).

Global inhibition of neural firing by application of tetrodotoxin (TTX) scales up excitatory synapses. Experimental support for the sliding threshold model comes primarily from studies in sensory cortices, where sensory deprivation alters the synaptic modification threshold to favor LTD (Kirkwood et al., 1996).

This is because synapses that receive activity that falls below the threshold for LTP will undergo LTD, while those receiving activity surpassing the threshold will express LTP (Cooper and Bear, 2012). This is a unique aspect of the sliding threshold model: it allows for LTD to occur even if the activity is not sufficient to induce LTP. However, the sliding threshold model is limited in its ability to account for changes in synaptic strength that are not dependent on neural activity.

In summary, synaptic scaling provides a complementary view to the sliding threshold model, allowing for LTD in the absence of neural activity. This suggests that synaptic scaling and the sliding threshold model are not mutually exclusive, but rather provide different mechanisms for regulating synaptic strength.

**DEMONSTRATION OF HOMEOSTATIC SYNAPTIC PLASTICITY IN VIVO**

Experience-dependent homeostatic synaptic plasticity has been demonstrated in various in vivo preparations (Whittington et al., 2014). The first experimental evidence came from studies on meta-plasticity showing that prolonged visual deprivation alters the induction threshold for LTD (Kirkwood et al., 1995, 1996). Dark-rearing is expected to reduce the overall activity in visual cortex, which decreases the induction threshold for LTD as predicted from the sliding threshold model (Figure 1A). Subsequent studies showed that increased activity reduced the induction threshold for LTD, which is consistent with the idea that synaptic modification thresholds shift in response to changes in neural activity.

While both sliding threshold and synaptic scaling models provide a homeostatic view that these two forms of homeostatic synaptic plasticity could operate, and provide evidence supporting a novel model of metaplasticity (Turrigiano and Nelson, 2004). In brief, prolonged inactivity leads to upsampling of excitatory synapses while prolonged activity leads to downsampling of synapses to maintain overall activity rate.

Initial experimental support for the synaptic scaling homeostasis model came from in vitro neuronal culture models, where activity was manipulated globally using pharmacological methods. Global inhibition of neuronal firing by application of tetrodotoxin (TTX) scales up excitatory synapses while increasing neuronal activity. Pharmacologically locking inhibition in isolated layers is key to understanding how synaptic scaling operates (O'Brien et al., 1998; Turrigiano et al., 1998).

While both sliding threshold and synaptic scaling models provide a similar homeostatic control over regulating synaptic strength, they differ in one key element: the sliding threshold model operates by altering the induction threshold for LTD, whereas synaptic scaling operates by altering the induction threshold for LTD/LTP. Hence, by nature, requires neuronal activity to manifest the synaptic changes. Therefore, even in the absence of neural activity, changes in the synaptic modification threshold can occur without neuronal activity, as seen in the experiments of Cooper and Bear (2012). In summary, synaptic scaling is a key mechanism in synaptic plasticity, providing a complementary view to the sliding threshold model.
Different models of homeostatic synaptic plasticity comparison of sliding threshold model (A,B) and synaptic scaling (C). Sliding threshold model posits that the synaptic modification threshold ($\theta_M$) changes as a function of past activity of a neuron. When integrated past activity is high $\theta_M$ slides up to a higher value ($\theta_{M0}$) promoting LTD, while with lower overall activity $\theta_M$ slides down to a lower value ($\theta_{M00}$) to preferential induce LTP. Expression of LTP or LTD as a consequence of sliding $\theta_M$ acts to provide homeostasis of the average neural activity. $\theta_M$ can slide via a horizontal shift (A), which is implemented by altering the induction mechanisms of LTP/LTD such as regulation of GluN2B-containing NMDARs. $\theta_M$ can also slide by a vertical shift (B), which is mediated by changes in the expression mechanisms of LTP/LTD such as alteration in AMPAR phosphorylation state. Synaptic scaling was initially reported to occur globally across all synapses. A key feature that allows preservation of information stored at individual synapses despite global adjustment of synaptic weights is via multiplicative scaling (C). Individual synaptic weights ($a_1, a_2, \ldots a_x$) are multiplied by a same scaling factor ($f$), which is greater than 1 for adapting to inactivity and less than 1 for adaptation to increased activity.

Input-specific homeostatic synaptic plasticity and distinct activity regime. There are specific considerations needed when implementing homeostatic regulation in intact circuits in vivo, such as a need to provide homeostasis in an input-specific manner. Sliding threshold model can easily accomplish input-specificity as depicted in panel (A). When overall activity of a neuron is reduced, such as due to loss of its major input, $\theta_M$ slides down. This causes previously weak Input 2 to cross the LTP threshold for synaptic potentiation, but leaves the less active input (Input 1) in the LTD range. Such input-specific adaptation allows the neuron to dynamically update its synaptic weights to process the most active input(s) in the context of its overall activity. We propose that sliding threshold and synaptic scaling operate across different activity regimes in vivo as shown in panel (B). Based on the advantage sliding threshold endows intact neural networks, such as always adapting to the most relevant inputs as shown in panel (A), we surmise that this is the dominant mode of homeostatic adaptation within most physiological range of activity. However, sliding threshold is less likely to be effect at providing homeostasis at extreme ranges of activity. For instance, (Continued)
with recent spine loss (Barnes et al., 2017). Based on these observations showing that sensory experience-dependent homeostatic synaptic plasticity (HSP) occurs in EPSCs, input-specific scaling is observed in V1 by recent evidence discussed below, we propose that the apparent synaptic scaling induced in vivo with sensory manipulations is actually a manifestation of sliding threshold metaplasticity (Turrigiano et al., 2019). Thus, the specific activity regime may influence the type of plasticity (Turrigiano et al., 1999).

**SPECIFIC CHALLENGES OF HOMEOSTATIC SYNAPTIC PLASTICITY IN VIVO**

One of the challenges of homeostatic synaptic plasticity operating in vivo is that not all inputs produce identical cortical neurons receive input-specific scaling (Barnes et al., 2017) from multiple sensory areas. For example, inputs from the primary visual cortex (V1) are also from the sensory area of the lateral geniculate nucleus (LGN). Multiple inputs from multiple sensory areas may recruit distinct computational models that input-specific homeostatic synaptic plasticity is suited to improve information processing (Coogan and Burkhalter, 1993; Dong et al., 2004; Ji et al., 2015; Marques et al., 2015) while other sensory areas do not (Lakatos et al., 2007; Iurilli et al., 2016; Subcortical areas (Rotella et al., 2016) are highly input-specific in terms of input activity. Therefore, homeostatic synaptic plasticity needs to occur in a way to preserve information storage and processing capacity. In vivo studies of sensory areas in which specific input activity is manipulated need to focus on functional input-specific control that is independent from each other.

Another unique challenge to study in vivo homeostatic plasticity is that not all sensory manipulations lead to the same changes. As mentioned above, the case of visual deprivation is major in the paradigm ranging from intraocular TTX injection, dark-rearing, and dark-exposure to nucelation and retinal lesions (Turrigiano et al., 1998; Desai et al., 2002; Goel et al., 2006; Goel et al., 2007; Le Bihan et al., 2012; Keck et al., 2013; Barnes et al., 2017). However, cortical neurons in visual areas are different in their responses to different manipulations (Keck et al., 2013; Le Bihan et al., 2012; King et al., 2016). Thus, branch-specific homeostatic adaptation would allow functional input-specific control that is independent from each other.

Mechanistically, scaling up and down on homeostatic plasticity is a distinct molecular signaling pathway correlated with phosphorylation of GluA1 on S845, synaptic appearance of Ca$^{2+}$-permeable AMPARs (Goel et al., 2006) and mGluR1 (Chokshi et al., 2019). While downscaling is independent on Arc (Goel et al., 2010) and GluR5 and (Homer 1A and 1B, Chokshi et al., 2019). Although GluA1-S845 is necessary for upscaling, GluA1-knockout is sufficient to recapitulate multiplicative scaling (Goel et al., 2011). Multiplicative change is a key feature of the scaling (Fig. 2C). Since the expression of mGluRs is caused by the homeostatic signaling in sensory neurons but not in all sensory neurons (Turrigiano et al., 1998). However, multiplicative scaling is only observed in early infancy development (P21 to P35) and infancy (10 to 12 months). As mentioned above, the case of visual deprivation is major in the paradigm ranging from intraocular TTX injection, dark-rearing, and dark-exposure to nucelation and retinal lesions (Turrigiano et al., 1998; Desai et al., 2002; Goel et al., 2006; Goel et al., 2007; Le Bihan et al., 2012; Keck et al., 2013; Barnes et al., 2017). However, cortical neurons in visual areas are different in their responses to different manipulations (Keck et al., 2013; Le Bihan et al., 2012; King et al., 2016). Thus, branch-specific homeostatic adaptation would allow functional input-specific control that is independent from each other.
Different activity regime may recruit distinct homeostatic synaptic plasticity in vivo

There is emerging evidence that different activity regimes may recruit distinct modes of homeostatic adaptation in vivo (Figure 2B). Bridi et al. reported that visual deprivation leads to metaplasticity mode of homeostatic adaptation in V1 (Bridi et al., 2018). Interestingly, silencing cortical activity more by pharmacologically increasing tonic inhibition produces synaptic scaling-like adaptation (Bridi et al., 2018). Of interest is that visual deprivation-induced metaplasticity is likely driven by increased spontaneous activity acting on GluN2B-containing NMDARs (Bridi et al., 2018). This is a counter to the conventional notion that sensory deprivation leads to loss of activity in the corresponding sensory cortex and that inactivity-driven homeostatic adaptation of this work suggests that sensory deprivation-induced homeostatic plasticity requires activity.

We also recently reported that dark exposure-induced upscaling of mEPSCs in V1/L2/3 is dependent on NMDAR activity (Rodriguez et al., 2019), which further corroborates the involvement of sliding threshold that acts on NMDAR-dependent LTD/LTP processes. Our current working model is that sensory deprivation-induced reduction in synaptic modification thresholds coupled with increased spontaneous activity potentiates synapses in a homeostatic manner in the visual system. Excitatory sensory inputs are increased in spontaneous activity and the L4 layer, NMDAR-dependent LTD/LTP processes, which further corroborates the involvement of sliding threshold that acts on NMDAR-dependent LTD/LTP processes. Our current working model is that sensory deprivation-induced reduction in synaptic modification thresholds coupled with increased spontaneous activity potentiates synapses in a homeostatic manner in the visual system. Excitatory sensory inputs are increased in spontaneous activity and the L4 layer.

The findings suggest that similar mechanisms may operate across sensory cortices.

While sliding threshold-mediated homeostatic adaptation has an advantage that it can easily implement input-specificity (Figure 2A), inputs that exhibit activity above threshold will produce potentiation, those falling below will depress. mEPSCs with minimal activity or activity at the threshold will not change. Such input-specific homeostatic adaptation has several advantages, such that visual cortex circuits are preferentially processed currently active inputs despite overall activity changes. Therefore, the cortical network, which dynamically configures for processing the most relevant information across cortex, can adapt activity to the circuit. We also note that input-specific homeostatic plasticity may be more prevalent in immature cortex (Goel and Lee, 2007) than in adult cortex (Linden et al., 2009). We further propose that network plasticity may be more prevalent in immature cortex than in adult cortex.

Different activity regime may recruit distinct homeostatic synaptic plasticity in vivo

**DIFFERENT ACTIVITY REGIME MAY RECRUIT DISTINCT HOMEOSTATIC SYNAPTIC PLASTICITY IN VIVO**

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AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct and intellectual contribution to the work and approved its publication.

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