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 innately alters the flow of information between neurons. Furthermore, activity-dependent synaptic plasticity, namely long-term potentiation (LTP) and long-term depression (LTD), create 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). A successful theory that allowed network stability developed by Leon Cooper’s group, the threshold for synaptic plasticity is controlled by integrated past neuronal activity...
In addition, sliding threshold model posits that scales up excitatory synapses (O'Brien et al., 1998; Turrigiano et al., 1998) without neural activity. Indeed, blocking all activity with TTX produces an LTD-like change in synaptic gain, unless the scale of operation is local as has been shown in some experimental preparations (reviewed in Turrigiano, 2008). In the following sections, we will discuss evidence from various in vivo preparations (Whittington et al., 2014). The first experimental evidence came from studies on metaplasticity showing that prolonged visual deprivation alters the induction threshold for LTD (Kirkwood et al., 1995) and dark-rearing expectantly reduces the overall activity in visual cortex (Hardingham et al., 2008). Prolonged reduction in activity leads to upscaling of excitatory synapses, which in turn increases intrinsic excitability and facilitates synaptic modification thresholds, favoring LTD (Kirkwood et al., 1996; Hardingham et al., 2008; Turrigiano, 1998).

Synaptic scaling is an alternative popular model that provides homeostasis by adjusting the synaptic gain. While the sliding threshold model was initially proposed to explain the development of neural activity and experience-dependent cortical plasticity, the premise of synaptic scaling was that activity regulates synaptic strength. Experimental support for sliding threshold model comes primarily from studies in sensory cortices, where sensory deprivation alters the synaptic modification threshold for LTD (Turrigiano and Nelson, 2004). In brief, prolonged inactivity leads to upscaling of excitatory synapses, which in turn increases intrinsic excitability and facilitates synaptic modification thresholds, favoring LTD (Kirkwood et al., 1996; Hardingham et al., 2008; Turrigiano, 1998).

While both sliding threshold and synaptic scaling provide similar homeostatic control by regulating synaptic strength, they differ in one key element: sliding threshold model operates by altering the induction threshold for LTD, while synaptic scaling operates by changing the intrinsic excitability of neurons. Homeostatic control is thus achieved by changing the intrinsic excitability of neurons (Bienenstock et al., 1982; Cooper and Bear, 2012). The key feature of the sliding threshold model is that the induction threshold for LTD is determined by past neuronal activity (Figures 1A, B). Specifically, high activity increases the threshold for LTD induction, which means most activity would fail to induce LTD. Synaptic modification thresholds are also homeostatically regulated by adjusting the synaptic gain (Bienenstock et al., 1982; Bear et al., 1987; Cooper and Bear, 2012). The key feature of the sliding threshold model is that the induction threshold for LTD is determined by past neuronal activity (Figures 1A, B). Specifically, high activity increases the threshold for LTD induction, which means most activity would fail to induce LTD. Synaptic modification thresholds are also homeostatically regulated by adjusting the synaptic gain (Bienenstock et al., 1982; Bear et al., 1987; Cooper and Bear, 2012).

In the following sections, we will discuss evidence from various in vivo preparations (reviewed in Turrigiano, 2008).

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 metaplasticity showing that prolonged visual deprivation alters the induction threshold for LTD (Kirkwood et al., 1995) and dark-rearing expectantly reduces the overall activity in visual cortex (Hardingham et al., 2008). Prolonged reduction in activity leads to upscaling of excitatory synapses, which in turn increases intrinsic excitability and facilitates synaptic modification thresholds, favoring LTD (Kirkwood et al., 1996; Hardingham et al., 2008; Turrigiano, 1998).

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Visual cortex has also been shown to demonstrate synaptic scaling in vivo for example via visual deprivation in both parasagittal transection of the visual cortex (Desai et al., 2002) and kainic acid injection in rats (Turrigiano and Nelson, 2004).

In the following sections, we will discuss evidence from various in vivo preparations (reviewed in Turrigiano, 2008).
FIGURE 1 | 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 \( \theta_M^0 \) promoting LTD, while with lower overall activity \( \theta_M \) slides down to a lower value \( \theta_M^{00} \) 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 \( a_1, \ldots, a_x \) 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.

FIGURE 2 | 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)
Figure 2 Continued

when activity levels are too low, even if the θr slides, there will be insufficient activity to activate NMDARs to drive potentiation of synapses. We suggest that NMDAR-independent synaptic scaling will be more effective at providing homeostatic adaptation with inactivity. At the other extreme, synaptic scaling will be much more effective at dampening overactive circuits, because it can globally reduce the strength of synapses.

Gao et al., 2010; He et al., 2012; Petrus and Lee, 2014). Dark-rearing (Goel et al., 2006) and enucleation (He et al., 2012; Barnes et al., 2017) leads to elevated mEPSCs Interestingly, an SVI upscaling of mEPSCs has a layer-specific sequential critical periods, where layer 1 (L1) (L2/3) (L3) (L4) (L5) (L6) (V1) (2P1) (2P3) (3P1) (4P3) (5P1) (6P3) (V1) (2P1) (2P3) (3P1) (4P3) (5P1) (6P3) (V1) (2P1) (2P3) (3P1) (4P3) (5P1) (6P3)

specific synaptic scaling induced in vivo with sensory manipulations is actually a manifestation of a sliding threshold metaplasticity (see Section “Different Activity Regimes May Recruit Distinct Homeostatic Synaptic Plasticity in vivo.”).

Specific Challenges of Homeostatic Synaptic Plasticity

One of the challenges of homeostatic plasticity operating in vivo is that not all inputs are identical. Cortical neurons receive diverse sets of inputs from multiple sources. For example, vision only receive inputs from the primary visual cortex (dLGN). But also receive inputs from the sensory areas (Lakato et al., 2007; Micu et al., 2012; Yoshitake et al., 2013; Ibrahim et al., 2016). Subcortical areas (Roth et al., 2016) and higher visual areas (Coogan and Burkhalter, 1993; Dong et al., 2004; Wang et al., 2015; Jarques et al., 2018) also receive sensory inputs (Wallace et al., 2016). Input diversity is a property of particular properties (Bark et al., other general properties. Are interconnected cortical networks inconceivable where that all inputs are equivalent and share the same levels of input activity? Here, homeostatic synaptic plasticity needs to occur in a way that preserves information storage and processing capacity for a diverse set of networks in which each particular neuron participates. Still, there is a need for computational modeling that input-specific homeostatic plasticity is much better suited to improve information processing than global synaptic scaling (Belle et al., 2017) for further discussion (see Eckel et al., 2017). In this particular study, the unitary homeostatic control was proposed as a dendritic branch pathway that involves several observations that are similar to input re-use and cluster on the same dendritic branch (Wilson et al., 2016). A branch-specific homeostatic adaptation would allow functional input-specific control that is independent from each other.

Another unique challenge is to study in vivo homeostatic plasticity in that not all sensory manipulations lead to the same changes. As mentioned above, the case of visual deprivation is a major paradigm ranging from intraocular TTX injection, dark-rearing, dark-exposure, and enucleation and retinal lesions (figure 1A) (Petrus and Lee, 2007). Despite this, other studies have shown that synaptic scaling in adult animals is not global but is limited to one subset of synapses. Consistently, with this interpretation, we reported that DE-induced upscaling of mEPSCs reflects potentiation of late lateral intracortical (IC) synapses, but feedforward (FF) synapses from layer 1 (P2/3) to layer 2/3 are immune to this type of plasticity (Petrus and Lee, 2015).

Similarly, downscaling of mEPSCs with visual experience was also limited to specific synapses (Chokshi et al., 2019). Such input-specific synaptic scaling is observed in layer 1.5 of V1 and the level of dendritic spine plasticity that was reported to be visual deprivation is in the nucleus of the lateral geniculate, but not in layer 2/3. Neurons in which specific dendritic branches with recent spine loss (Barnes et al., 2017) Based on these observations showing that sensory experience-dependent homeostatic plasticity in mEPSCs is input-specific, it is clear that recent evidence discussed below would propose that the apparent synaptic scaling induced in vivo with sensory manipulations is actually a manifestation of a sliding threshold metaplasticity (see Section “Different Activity Regimes May Recruit Distinct Homeostatic Synaptic Plasticity in vivo.”).

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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. (2018) reported that visual deafferentation leads to metaplasticity mode of homeostatic adaptation via 1) silenced cortical activity—more by pharmacologically increasing tonic inhibition—producing synaptic scaling—like adaptation (Bridi et al., 2018). Of interest is that visual deprivation-induced metaplasticity likely driven by increased spontaneous activity acting on GluN2B-containing NMDARs. This discovery counters the conventional notion that sensory deprivation leads to loss of activity in the corresponding sensory cortex and that inactivity-driven homeostatic adaptation of his work suggests that sensory deprivation-induced homeostatic plasticity requires activity. For instance, in the final form of elevated spontaneous activity we have recently reported that dark-exposure induced upscaling of mEPSCs in V1 L2/3 dependent on NMDAR activity (Rodriguez et al., 2019). Which further corroborates the involvement of sliding threshold that acts on NMDAR-dependent LTP/LTD processes. Our current working model is that sensory deprivation-induced reduction in synaptic modification thresholds coupled with increased spontaneous activity potentiates synapses to mediate homeostatic increases in excitatory synaptic gain. Increased spontaneous activity has been reported with auditory deprivation (Kotak et al., 2005) and infraorbital nerve transection that potentiates synapses in barrel cortex (also increases GluN2B-containing NMDARs; Chung et al., 2017). These findings suggest that similar mechanisms may operate in cross sensory cortices.

Sliding threshold mediated homeostatic adaptation has an advantage that it can be easily implemented in input-specificity (Figure 2A). Inputs that exhibit activity above the threshold will produce potentiation, those falling below will depress. Inputs with minimal activity foractivity of the threshold will not change. Such input-specific homeostatic adaptation is a more advanced idea that will allow the circuit to preferentially process currently active inputs despite overall activity changes. Therefore, the cortical network can dynamically reconfigure for processing the most relevant information in the context of overall activity in the circuit (Whitford et al., 2014; also see Blaisdell et al., 2008). Also of note is that input-specific homeostatic plasticity may be more prevalent in immature cortex (Goel and Lee, 2007; Ranson et al., 2012; Petrus et al., 2015; Barnes et al., 2017; Choksi et al., 2019).

While sliding threshold provides homeostasis with sensory manipulation paradigms, synaptic scaling seems to also be present in vivo but at high-extreme activity ranges (Figure 2B). For example, reducing cortical activity by pharmacologically increasing tonic inhibition leads to upscaling of mEPSCs, which is independent on NMDARs (Bridi et al., 2018). We have observed that synaptic scaling may also operate when neural activity is increased to the extreme level of less functional state under either extreme activity regimes. Sliding threshold may be highly effective. For example, under extremely low activity, venetian blinds synaptic modification thresholds cede down, thereby maintaining sufficient level of activity to drive LTP for the homeostatic NMDAR-independent plasticity, such as synaptic scaling. May be better suited for synaptic adjustments under this condition. Similarly, when there is extremely high neural activity across all inputs, as would occur during seizures, having input-independent global synaptic scaling is likely more efficient way of amplifying activity.

Conclusion

We summarized that specific challenges faced when homeostatic plasticity operates in intact circuits in vivo with diverse sets of inputs. We propose that sliding threshold mediated cross activity range(s) that can recruit NMDAR-dependent input-specific synaptic plasticity to maintain optimal processing of most relevant information despite overall changes in activity, while synaptic scaling may operate at extreme activity ranges of acutely failsafe.
AUTHOR CONTRIBUTIONS

Both authors designed and performed substantial portions of the experiments and intellectual contributions to the work, and both authors have approved publication of this work.

REFERENCES


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