

What goes up must come down: homeostatic synaptic plasticity strategies in neurological disease

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Brain activity levels are tightly regulated to minimize imbalances in activity state. Deviations from the normal range of activity are deleterious and often associated with neurological disorders. To maintain optimal levels of activity, regulatory mechanisms termed homeostatic synaptic plasticity establish desired 'set points' for neural activity, monitor the network for deviations from the set point and initiate compensatory responses to return activity to the appropriate level that permits physiological function [1,2]. We speculate that impaired homeostatic control may contribute to the etiology of various neurological disorders including epilepsy and Alzheimer's disease, two disorders that exhibit hyperexcitability as a key feature during pathogenesis. Here, we will focus on recent progress in developing homeostatic regulation of neural activity as a therapeutic tool.

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Homeostatic synaptic plasticity in epilepsy: too much of a good thing?

Epilepsy is characterized by repeated and spontaneously occurring seizures [3,4], but we still do not fully understand the mechanisms underlying the development of epilepsy (epileptogenesis). The temporal lobe is particularly vulnerable, with mesial temporal lobe epilepsy (mTLE; affecting hippocampus, parahippocampal gyrus and amygdala) being the most prevalent seizure condition in adults [3]. Classically, the view has been that an initial insult (or first seizure episode in some animal models) leads to a latent period that can induce a prolonged period of hypoactivity, followed weeks later by the emergence of epileptiform activity. For example, transient hypoactivity has been reported after epileptogenic insults such as traumatic brain injury [5,6]. Indeed, even after acute generalized seizures, postictal depression, in which the patient experiences sedation and confusion, is a common finding, and has been associated with profound release of opioid peptides [7]. Todd's paresis, a temporary loss of function in a region impacted by a seizure, may also occur and can last for hours to days before resolving. Persistent changes in neuronal activity induce homeostatic compensation, which can manifest in numerous ways depending on the particular context. These mechanisms include alterations in the number, size and strength of synapses (homeostatic synaptic plasticity [HSP]) as well as a variety of other forms of regulating excitability [1,2]. Chronic hypoactivity following seizures is predicted to induce homeostatic strengthening of excitatory synapses in order to restore network activity; a phenomenon that has been observed in some rodent seizure models [8]. Thus, aberrant or dysfunctional homeostatic compensation could contribute to the emergence of spontaneous recurrent seizures through an overshooting 'rebound' effect. Homeostatic strategies, described below, may be able to rescue hypoactivity during the latent period or dampen the ensuing rebound effect, and thereby potentially alter the course of epileptogenesis.

Acute HSP strategies for epilepsy: closing the loop

Closed-loop control is a form of homeostatic regulation, often employed in man-made engineering processes, in which a system output is monitored, compared against a desired set point value and any deviations are corrected by a compensatory adjustment [2]. This type of bioengineering approach has been successfully employed to combat

seizures by combining EEG recordings (the sensor) with a regulator. Electrical stimulation has been used as a regulator in both animal models and in human patients [9,10]. More recently, cell-type-specific expression of light-gated cation channels (i.e., optogenetics) in GABAergic neurons have been used as regulators in animal models [11]. In these ‘closed loop’ or ‘responsive neurostimulation’ paradigms, EEG detection of seizure activity automatically activates light delivery via a fiber optic cable, immediately terminating seizures in freely moving mice [11]. This strategy has now been used in a wide variety of brain regions (e.g., hippocampus, cerebellum, thalamus) [11–14] demonstrating that diverse components of seizure circuits may be harnessed to suppress pathological activity. A drawback to this approach is the invasive nature of the procedure using fiber optics [15]); however, with advances in optogenetics using far-red excitation wavelengths, it may be possible theoretically to activate interneurons by light transmitted through the intact cranium [16]. Another caveat is that these procedures use operational definitions of seizure (aberrant activity in EEG) for detection and termination, and therefore may miss some important aspects of pathogenesis or cause unforeseen ramifications. The degree to which closed-loop interventions (electrical, optogenetic or other) may be harnessed to suppress epileptogenesis, as compared with suppression of seizures after they have already emerged, remains an open and interesting question.

Chronic HSP strategies for epilepsy: fighting fire with fire

The most commonly used antiseizure drugs (ASDs) currently all operate on the same general principle: to decrease neuronal firing either directly or indirectly, through blockade of cation channels or enhancement of GABA-mediated inhibition. Thus, acute administration of ASDs acts in a powerfully anticonvulsant manner. However, a third of epilepsy patients are not satisfactorily responsive to ASDs, and these medications do not alter the progression of epileptogenesis or modify disease course once epilepsy has developed [3,17]. Another important caveat from a homeostatic standpoint is that chronic inhibition of neuronal activity produces a compensatory increase in excitatory synaptic strength on hippocampal pyramidal neurons [2,18,19]. The prediction from HSP is that chronic, long-term administration of ASDs would eventually increase excitatory drive in neurons, which would manifest upon drug removal, again, leading to an opposite rebound effect that may explain the refractory nature of some patients to ASD treatment. Along these lines, experimental manipulations that suppress neuronal activity (e.g., lidocaine administration) have been shown to produce a kindling phenomenon [20]. Similarly, rebound seizures after precipitous withdrawal of benzodiazepines have typically been attributed to homeostatic changes at the level of GABA_A receptor expression; however, chronic diazepam also induces HSP upregulation of the size and strength of MF-CA3 synapses *in vivo* [18], suggesting that this may also play into the emergence of seizures after drug withdrawal.

From homeostatic principles, it may be that rather than chronically inhibiting activity, an alternative approach in some cases may be to persistently increase activity, as chronic hyperexcitation is known to cause compensatory weakening of excitatory synapses [21]. Thus, moderate overexcitation could be used to counter seizures, to fight fire with fire. This counterintuitive strategy has garnered some experimental support. For instance, vagus nerve stimulation is used as a treatment of epilepsy [22]. We hypothesize that this action may be due to repeated mild stimulation of projections to the hippocampus and amygdala areas implicated in the generation of seizure activity, thereby activating endogenous homeostatic downregulation of neurons in those target regions. It is interesting to note that even acute, but subconvulsant hyperactivity within the hippocampus may exert anticonvulsant effects. For example, intra-hippocampal microinjection of GABA antagonist or glutamate agonists seem to potently suppress evoked seizures, suggesting that circuit level closed-loop mechanisms may also exist within the hippocampus to restrain pathological overactivity (AUTHOR’S UNPUBLISHED OBSERVATIONS). The effect of long-term implementation of these stimulation protocols on altering disease progression remains to be determined.

Engaging the hippocampal ‘homeostatic brake’

Global excitation or inhibition of the brain may be effective in controlling seizures, but not optimal in terms of preserving normal brain functioning. Indeed, current ASDs have significant adverse effects on the ability of patients to perform daily activities of life. A more surgical approach would be to identify and target specific systems that regulate homeostatic adaptation, which could lead to fewer side effects. Toward this goal, our recent work has shown that specific neurons and specific subsets of synapses, are more homeostatic than others. In other words, some neurons initiate strong HSP mechanisms at excitatory synapses following perturbations in activity, whereas other neuron types seem to respond less robustly [18]. One prominent regulatory locus lies at the synapses between mossy fibers (MF) of the dentate gyrus (DG) and pyramidal neurons of area CA3. We found that chronic

changes in network activity caused homeostatic adaptation specifically in the MF-CA3 synapse, when analyzed both morphologically and functionally [18]. Thus, this synapse performs a designated role as a homeostatic ‘gain control’ mechanism for hippocampal circuits.

The MF-CA3 synapse has properties that make it particularly attractive as a homeostatic control point. The CA3 network is a highly interconnected system which functions to associate cortical inputs, but which by its recurrent nature is also highly prone to seizure activity [23]. Thus, inputs to CA3 from DG must be strictly gated to prevent runaway excitation of the CA3 autoassociative network. Additionally, MF-CA3 connections are very powerful, often comprised of many synapses onto the same site, and could effectively gate inputs from DG to CA3 to prevent seizure generation in CA3 recurrent networks [24]. MFs also innervate interneuron populations which control CA3 networks, some of which are selectively lost in epilepsy [25]. Thus, dysregulation of the MF inputs could lead to dramatic alterations in network activity, but if harnessed could also provide a powerful means to control activity, acting as a ‘homeostatic brake’.

To further test the role of the MF-CA3 synapses in regulating epileptogenesis, we examined the role of opioid receptors. The MF tract is highly enriched in endogenous opioid peptides, the levels of which are markedly regulated by neuronal activity [26]. By testing various agonists and antagonists of different classical opioid receptors, we found that kappa opioid receptor (KOR) signaling was both necessary and sufficient to induce HSP in cultured hippocampal neurons *in vitro*. Furthermore, chronic administration of low dose KOR antagonist norbinaltorphimine (nor-BNI) dampened seizure development in electrical and chemical kindling paradigms [27]. This finding is interesting in two ways. First, KOR antagonists are known to exert acute excitatory actions; thus this antiseizure effect of chronic nor-BNI is another example of ‘fighting fire with fire’. Second, the nor-BNI treatment was given after each kindling episode, suggesting that the therapy could be administered even after an initial insult during the latent period to potentially modify disease progression.

Future studies will test whether similar approaches may be fruitful in epilepsy models featuring spontaneous development of seizures. This MF-CA3 ‘gain control’ synapse may also offer additional therapeutic targets; for instance, the presynaptic protein synaptoporin, which is selectively enriched in MF terminals, is necessary to induce homeostatic upregulation of MF-CA3 synapses *in vitro* in response to chronic action potential blockade by tetrodotoxin [18]. Reducing the expression of synaptoporin *in vivo* may prevent the ‘rebound’ strengthening of neuronal activity and hence reduce the propensity to develop seizures in the first place.

Hyperexcitability in Alzheimer’s disease: an epilepsy connection?

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by dementia and progressive memory loss, and is associated with the accumulation of hallmark A β plaques and neurofibrillary tangles (NFTs) in the brains of AD patients [28,29]. A β is produced from the cleavage of the amyloid precursor protein (APP) by β - and γ -secretases, whereas NFTs are comprised chiefly of hyperphosphorylated tau, a microtubule-associated protein. The mechanisms underlying the disease process are still not well understood and are intensely under investigation, but it is generally thought that aggregation of A β initiates a cascade of events that causes dysfunction in tau and eventually culminates in profound neurodegeneration in the late stages of AD [28,29]. It is noteworthy that AD patients have an increased incidence of epileptic seizures, especially in those with early onset familial AD mutations [30–33], with an estimated 10–22% of AD patients developing epilepsy. In this regard, it has been observed that hyperactive neurons are prevalent in presymptomatic AD patients and transgenic mouse models [34–41], which may contribute to increased seizure susceptibility [37,42].

The extent of seizures may actually be underappreciated in AD patients due to the phenomenon of ‘silent’ seizures. Overt convulsive events are infrequent in AD, and typical AD symptoms may interfere with the detection of nonconvulsive seizures [31,43,44]. In this regard, a recent study described two AD patients for which no seizure activity could be detected by EEG, but intracranial electrodes were able to detect significant subclinical seizure activity originating from the mesial temporal lobe [45]. Treatment of one of these patients with levetiracetam, a widely used ASD that is orally available and readily crosses the blood–brain barrier [46], reduced temporal lobe seizure activity and almost completely abrogated episodes of extreme confusion for at least 1 year [45]. Although this study is limited by an extremely small sample size, levetiracetam also has been shown by others to dampen abnormal hyperactivity in the hippocampal DG and CA3 regions, rescue cognitive deficits in AD models and improve memory in patients with mild cognitive impairment, the earliest diagnosed stage of AD [47–49]. Taken together, these data suggest that seizure in AD not only contributes to pathological symptoms, but also that common antiepileptic drugs may have significantly positive effects in some cases. Additional research is required to elucidate

the mechanism of action of levetiracetam and related compounds in AD, and further investigation with clinical trials will be needed to explore the long-term benefits of ASDs for AD patient populations [50].

Homeostatic synaptic plasticity & AD

A caveat to the chronic use of levetiracetam for AD is that this approach may lead to homeostatic synaptic strengthening and an opposite rebound effect that could exacerbate hyperactivity, as we discussed for other ASDs in epilepsy. However, levetiracetam is atypical in mechanism as it modulates neurotransmitter release rather than directly impacting neuronal excitability. Examination of levetiracetam *in vitro* and *in vivo* for the ability to induce HSP is thus of particular interest. Even in the absence of therapies, hyperactive neurons in early AD would be expected to trigger endogenous homeostatic synaptic downregulation as a protective mechanism to reduce hyperexcitability and attendant excitotoxicity. One way in which such endogenous closed-loop control could be manifested is through excitatory synapse loss. Indeed, glutamatergic synapse loss is a hallmark feature of early AD which occurs prior to the development of A β plaques and NFTs, and which more closely correlates with symptomatic progression in patients [51–55]. These observations are consistent with compensatory HSP mechanisms as an attempt to bring balance to the network.

Excitatory synapse loss may be related to the production of A β itself, which has properties of a homeostatic regulator. Neuronal activity has been shown to upregulate β -secretase processing of APP and subsequent generation and secretion of extracellular A β [56–60]. A β levels seem to have a hormetic effect on neuronal transmission resulting in both inhibitory and excitatory effects depending on its extrasynaptic concentration [55,61,62]. Low concentrations of extracellular A β in the picomolar range lead to increased neuronal potentiation and network excitability, whereas higher A β concentrations (nanomolar to micromolar range) lead to decreased potentiation, as well as long-term depression (LTD) and loss of dendritic spines [37,57,61]. This bidirectional characteristic is ideal for a homeostatic regulator of synaptic activity, during hypoactivity (and hence low A β concentrations), A β has a stimulatory effect, while strong neuronal activity induces more A β , which then acts to restrain excitation. Hyperexcitation during AD may initially be compensated for by adjustments in synaptic strength, followed by synapse loss only after significant synaptic remodeling has occurred [28].

During AD, the physiological effects of A β may become subverted due to its aggregation into pathological soluble oligomers, which have been shown to induce hyperexcitability in the vicinity of amyloid plaques [34,63]. Thus, increases in neuronal activity trigger A β production and, in turn excess oligomeric A β further promotes excitation. In contrast to the typical homeostatic closed-loop negative feedback control, this dysregulation leads to a positive feedback loop, which would be predicted to become self-perpetuating and may drive early stage pathogenesis.

Role of Polo-like kinase 2 in APP processing

To interrupt the putative positive feedback loop of hyperexcitation in AD, one strategy is to decipher and modulate the mechanisms that control the activity-dependent formation of A β . A potential molecular link between neuronal activity and APP β -processing is the homeostatic regulator Polo-like kinase 2 (Plk2). Similar to A β , Plk2 is induced in response to sustained network overactivity and functions to weaken excitatory synapses [8,21,64,65], leading to the hypothesis that Plk2 might be involved in A β production and/or participate in shared functions. We recently demonstrated that Plk2 is required for neuronal activity-induced production of A β , mediated by direct phosphorylation of APP by Plk2 at two sites, threonine-668 and serine-675 [58]. Importantly, both sites must be blocked in order to see a change in APP surface expression and β -secretase processing, providing an explanation for the lack of effect of the single threonine-668 to alanine mutation using knock-in mice [66]. Thus, combinatorial phosphorylation of APP is triggered by neuronal hyperexcitation through Plk2, leading to APP endocytosis, cleavage, and subsequent A β secretion. These data further implicate APP/A β as potential components of the HSP machinery as part of their normal physiological functions, and present Plk2 as an attractive novel target for AD drug therapy.

Future perspective

Although it is still unknown whether HSP mechanisms are related to the etiology of neurological disorders including epilepsy and AD, tantalizing clues are beginning to emerge that suggest this may be the case (Figure 1). If so, understanding these systems may allow us to harness the power of endogenous hippocampal gain control to reduce hyperexcitability and alter disease progression. Within the next decade, we may begin to see some of

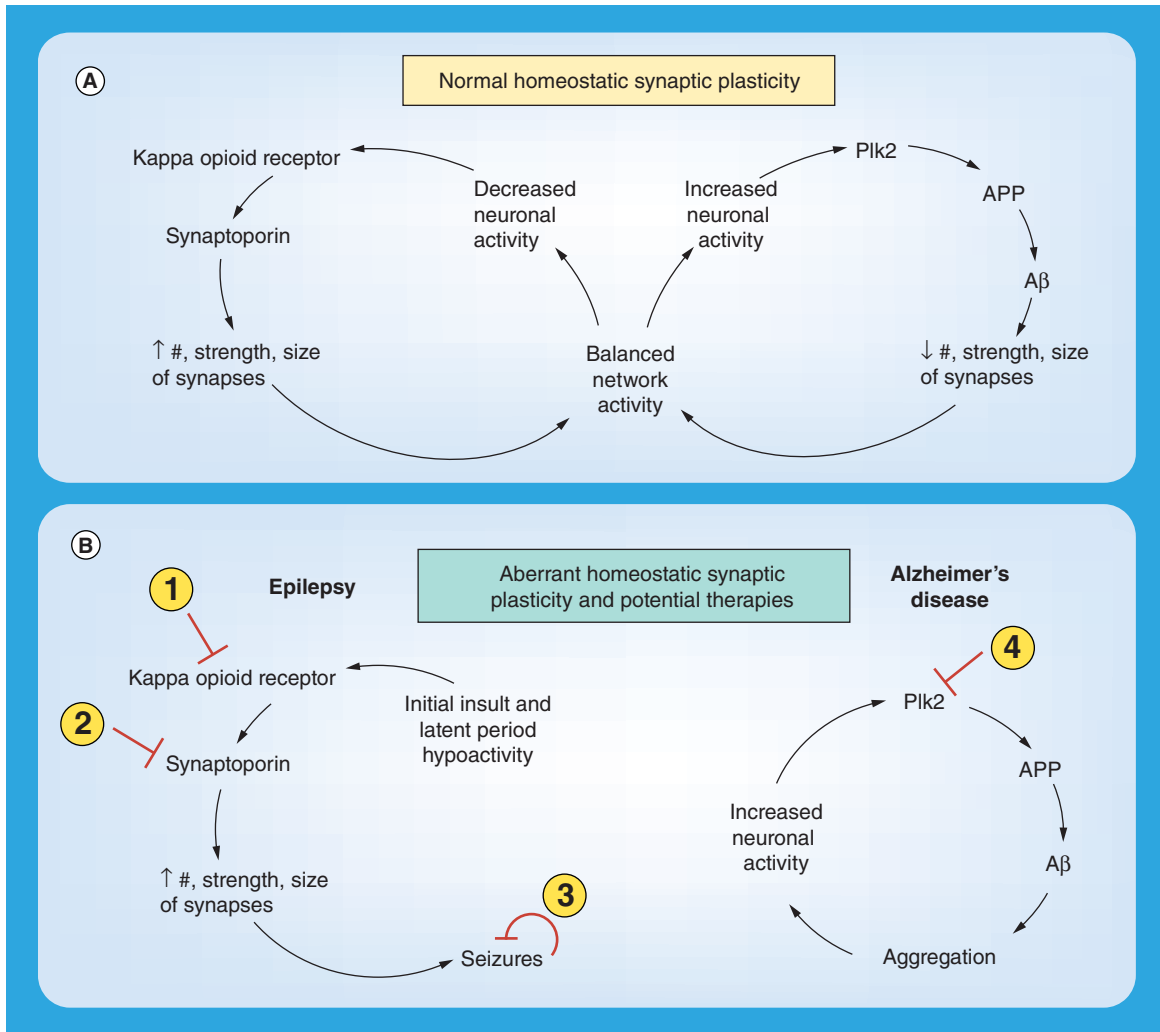


Figure 1. Mechanisms of homeostatic synaptic plasticity that are discussed in the text. (A) Normal homeostatic synaptic plasticity. On the left are pathways involved in homeostatic upregulation in response to chronic hypoactivity and on the right are those involved in downregulation following persistent hyperactivity. Negative feedback compensation alters synaptic number, strength or size in order to return network activity to an optimal, balanced level. Multiple homeostatic mechanisms have been identified and only a subset is depicted here. **(B)** Proposed mechanisms of aberrant homeostatic plasticity that may contribute to neurological disorders. On the left is a hypothetical pathway that may promote development of epilepsy, in which an initial insult leads to a latent period of hypoactivity, triggering overcompensation and excessive synaptic strengthening due to dysfunctional homeostatic machinery that ultimately leads to seizures. Therapeutic strategies for epilepsy could be to inhibit: kappa opioid receptors or synaptoporin function to prevent development of seizures or perform closed-loop bioengineering control to terminate seizures acutely. On the right is a proposed model for pathogenesis of Alzheimer's disease in which aggregation of A β leads to hyperactivity of neurons rather than downregulation as in the normal condition. Hyperexcitation leads to further production of A β via Plk2, forming a positive feedback, amplifying loop instead of a negative feedback control system. A therapeutic approach to address this model could be to inhibit Plk2 activity and interrupt the vicious cycle.

these ideas reaching the clinic, for example, implantable closed-loop control systems or drugs targeting putative homeostatic components such as KORs, synaptoporin or Plk2. These principles may also be useful for mitigating other neurological and neurodegenerative disorders, including Parkinson's and Huntington's diseases as well as primary tauopathies.

Conclusion

HSP mechanisms seek to maintain brain activity levels in an optimal and balanced state that allows for optimal physiological function. Further studies are needed to elucidate the myriad of homeostatic pathways that govern neuronal circuits and begin to appreciate the consequences of perturbing these systems. Deepening our understanding of these mechanisms may shed light on a host of neurological disorders that feature imbalanced neural activity. However, it is important to proceed cautiously, keeping in mind that for every action there is an opposite reaction, which, especially in the context of HSP, can lead to unintended consequences due to chronic administration of therapeutics.

Executive summary

Homeostatic synaptic plasticity mechanisms maintain brain activity within a 'normal' range of activity

- These mechanisms can include changes in the number, size and strength of synapses.

Failure of homeostatic synaptic plasticity mechanisms may result in network activity dysregulation after seizures

- Periods of hypoactivity in brain regions affected by a seizure can lead to synaptic strengthening and subsequent increase in general network activity that may contribute to the development of epileptiform activity.

Harnessing homeostatic regulation could be a promising avenue of research for the treatment of epilepsy

- Closed-loop control using electrical stimulation to correct aberrant network activity can decrease seizures in some patients.
- To engage homeostatic synaptic plasticity (HSP) mechanisms, mild persistent overexcitation leading to synaptic weakening may be effective for long-term seizure reductions.
- Engagement of HSP mechanisms in synapses that have been shown to demonstrate significant homeostatic remodeling, rather than attempting to modulate activity in the entire brain could be a more effective treatment paradigm.

Dysregulation of network activity & HSP mechanisms may also be seen in Alzheimer's disease

- Increased clinical and subclinical seizure activity that could cause exacerbated symptoms has been observed in some Alzheimer's disease patients.
- Extracellular A β concentrations, which are regulated by neuronal activity, have been shown to cause hyperexcitability at low concentrations and synaptic depression and spine loss at high concentrations.
- Regulating production of A β may be an effective way to harness this potentially aberrant HSP mechanism.

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