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Cortical stimulation for treatment of neurological disorders of hyperexcitability: a role of homeostatic plasticity

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Abstract

Hyperexcitability of neural network is a key neurophysiological mechanism in several neurological disorders including epilepsy, neuropathic pain, and tinnitus. Although standard paradigm of pharmacological management of them is to suppress this hyperexcitability, such as having been exemplified by the use of certain antiepileptic drugs, their frequent refractoriness to drug treatment suggests likely different pathophysiological mechanism. Because the pathogenesis in these disorders exhibits a transition from an initial activity loss after injury or sensory deprivation to subsequent hyperexcitability and paroxysmal discharges, this process can be regarded as a process of functional compensation similar to homeostatic plasticity regulation, in which a set level of activity in neural network is maintained after injury-induced activity loss through enhanced network excitability. Enhancing brain activity, such as cortical stimulation that is found to be effective in relieving symptoms of these disorders, may reduce such hyperexcitability through homeostatic plasticity mechanism. Here we review current evidence of homeostatic plasticity in the mechanism of acquired epilepsy, neuropathic pain, and tinnitus and the effects and mechanism of cortical stimulation. Establishing a role of homeostatic plasticity in these disorders may provide a theoretical basis on their pathogenesis as well as guide the development and application of therapeutic approaches through electrically or pharmacologically stimulating brain activity for treating these disorders.

Keywords: *homeostatic plasticity*, *epilepsy*, *neuropathic pain*, *cerebral cortex*, *hyperexcitability*, *brain injury*, *tinnitus*, *cortical stimulation*

Introduction

Neurological disorders exhibit not only symptoms of functional deficits such as loss of sensation, weakness and paralysis, and poor cognitive function, but also abnormal functions such as pain, epilepsy, tinnitus, and phantom sensation. A key pathophysiological feature of these symptoms of abnormal functions is excessive activity and hyperexcitability of certain related subcortical pathways and cerebral cortex (Eggermont, 2005; Badawy et al., 2009; Latremoliere and Woolf, 2009). Correspondingly, the current treatment strategy for these neurological disorders is to reduce excitability and enhance inhibition. Paradoxically, brain stimulation that enhances neuronal activity is also found to be effective for treating these conditions (De Ridder et al., 2007; Morrell, 2011; Treister et al., 2013). Although various mechanisms such as activation of inhibitory circuits have been proposed to explain such effect, the direct effect of brain stimulation on the stimulated circuit is not well understood. Because these hyperexcitable neurological disorders usually start with acute or chronic damage and degeneration of brain or loss of afferent input, a homeostatic plasticity mechanism may play a role in the development and maintenance of brain hyperexcitability, which supports that activity stimulation can control neurological symptoms by reducing aberrant homeostatic hyperexcitability. Indeed, results from recent studies support a role of homeostatic plasticity in the mechanisms of neuropathic pain, acquired epilepsy, and neuropathic pain, which may support the development of novel therapeutic treatments for these neurological disorders. Here we briefly review recent progress in this direction and discuss future perspective. We have performed a PubMed search of articles published between January 1975 and July 2018 on homeostatic plasticity or cortical stimulation in combination with acquired epilepsy, neuropathic pain, or tinnitus.

Development of Homeostatic Hyperexcitability after Injury or Sensory Deprivation

Homeostatic plasticity is the ability of neural network to maintain a relatively constant level of firing rate in response to an imposed activity increase or decrease (Turrigiano et al., 1998). When a cortical network loses activity or input, it responds with compensatory increases in excitatory synaptic strength and intrinsic excitability, and/or a reduction in synaptic inhibition so that a set level of activity is maintained (**Figure 1A**) (Turrigiano et al., 1998; Davis and Bezprozvanny, 2001). Many neurological diseases feature hyperexcitability. However, such hyperexcitability is often developed form initial loss of neurons and synapses. Deprivation of peripheral input by activity blockade, amputation, or nervous lesion has been shown to cause homeostatic hyperexcitability of the cortical network in developing and adult brain. Therefore, development of cortical hyperexcitability that underlies various neurological disorders may be driven and maintained by abnormal homeostatic plasticity in response to initial lesions and loss of activity. Furthermore, because the primary lesion or pathology in the etiology of these neurological disorders (*e.g.*, spinal cord injury or brain injury) is often permanent or progressive, such homeostatic compensation is likely a constant or progressive process so that the deafferented cortex can maintain a set level of activity. Although homeostatic plasticity has been extensively studied in cultured neurons, brain slices, and more recently in the visual cortex *in vivo* (Echegoyen et al., 2007; Goel and Lee, 2007; Hengen et al., 2013; Keck et al., 2013), its role in pathological conditions has been demonstrated only recently.

Acquired epilepsy

Acquired epilepsy usually develops following an initial insult such as traumatic brain injury (TBI) or status epileptics. Brain injury, particularly severe TBI and penetrating TBI, causes neuronal death, tissue damage, and an initial loss of activity in surviving neurons (Alves et al., 2005). Indeed, lower action potential firing rates are recorded in TBI patients, the lateral fluid percussion model of TBI in rats, and an undercut model in cats *in vivo* (Timofeev et al., 2000; Alves et al., 2005). Neuronal activity is also depressed following brain ischemia (Heiss et al., 1976). Computational and experimental studies suggested that such activity loss is a driving force leading to epileptogenesis (Houweling et al., 2005; Dinocourt et al., 2011; Subramanian, 2011). In support of this idea, pharmacological blockade of neuronal activity of hippocampal neurons *in vitro* or *in vivo* for a few days leads to hyperexcitability with increased glutamatergic transmission, decreased GABAergic synaptic inputs, and epileptogenesis (Trasande and Ramirez, 2007). Likewise, chronic blockade of activity with tetrodotoxin or a lesion to the developing hippocampus produces chronic focal seizures accompanied by axon sprouting and increased intrinsic excitability (McKinney et al., 1997; Bausch et al., 2006).

Tinnitus

Tinnitus is the perception of a sound in the absence of acoustic stimulation. Cochlear damage and hearing loss can lead to tinnitus and abnormally increased spontaneous firing rates and synchronization of neurons in the auditory pathway, including the primary auditory and associated cortices (Elgoyhen et al., 2015). Homeostatic plasticity has been proposed to be responsible for hyperexcitability in auditory pathway in tinnitus (Yang et al., 2011). A computational study suggested that homeostatic compensation leads to hyperactivity of the model neurons when a normal ratio between mean and spontaneous firing rate of the auditory nerve is decreased due to a loss of outer hair cells or damage to hair cell stereocilia. Homeostasis can also amplify non-auditory inputs, which then contribute to hyperactivity (Schaette and Kempter, 2006). In a high-frequency hearing loss model, it was shown that neurons in the auditory cortex that represent the hearing-loss frequencies have reduced inhibitory synaptic transmission but unaltered excitatory synaptic transmission, and there is behavioral signs of tinnitus with the pitch in the hearing-loss frequency range. In contrast, neurons in the normal low-characteristic frequency zone have enhancement in both excitatory and inhibitory synaptic transmissions (Yang et al., 2011).

Neuropathic pain

Neuropathic pain occurs as a consequence of a primary lesion or disease that affects the somatosensory nervous system. Its development is believed to involve diverse mechanisms including changes in ion channels and receptors, inflammation, immune response, loss of inhibition, synaptic plasticity, and circuit reorganization (Latremoliere and Woolf, 2009). Synergic interactions among them contribute to peripheral and central sensitization, leading to hyperexcitability and ectopic firing of the nociceptive pathways. These electrophysiological changes reduce pain threshold and contribute to hyperalgesia and allodynia of neuropathic pain. Because development of neuropathic pain reflects a transition from an initial loss of neuronal activity due to a primary lesion (*e.g.*, nerve or spinal cord injury [SCI]) to a state of hyperexcitability and eventual paroxysmal discharges of the neuronal network, this process is reminiscent of homeostatic regulation. Deprivation of peripheral input by activity blockade, amputation, or nervous lesion has been shown to cause homeostatic hyperexcitability of thalamic or cortical network in developing and adult brain (Wang and Thompson, 2008; Xiong et al., 2017). SCI results in slower and more silent overall cortical spontaneous activity in the deafferented cortex as well as in the neighboring cortex during the earlier time period, representing a switch to a network state of slow-wave activity (Boord et al., 2008). In

tibial nerve injury model of neuropathic pain, optical imaging of voltage sensitive dye revealed increased optical intensity and an enlarged area of activation in the primary somatosensory cortex (S1) of neuropathic rats during electrical stimulation (Cha et al., 2009).

Cortical Stimulation for Controlling Hyperexcitability

The hyperexcitability of neural network in epilepsy, tinnitus, and neuropathic pain naturally leads to a treatment principle that attempts to suppress such hyperexcitability through inhibiting excitatory activity or enhancing inhibition. Indeed, this principle underlies current treatment strategy for controlling neurological disorders featuring abnormal hyperexcitability (**Figure 1B**). However, if hyperexcitability is induced and maintained by homeostatic plasticity in response to a loss of neuronal activity or afferent input after brain injuries or sensory deprivation, then stimulating neuronal activity should promote compensatory capability, reduce homeostatic plasticity, and prevent or control the symptoms. In other words, stimulating cortical activity will relieve the constant burden of homeostatic regulation so that activity of neural circuits may reverse to a relatively normal activity state (**Figure 1B**). Evidence from clinical and animal studies supports that cortical stimulation is indeed effective in the neurological diseases discussed above.

Acquired epilepsy

Treatment of cultured hippocampal slice with bicuculline for one week greatly diminishes the intensity of epileptiform activity that could be induced. Cannabinoid antagonists and alpha (2)-adrenoceptor antagonist atipamezole are both proconvulsant, but their application immediately after brain insults prevents the development of hyperexcitability or reduces seizure frequency and severity in animal models of epilepsy (Pitkanen et al., 2004; Armstrong et al., 2009). Cortical electrical stimulation is effective in enhancing neuronal plasticity and synaptic reorganization after TBI, reducing bursting activity in neuronal culture *in vitro*, and controlling partial seizures in drug resistant patients (Demirtas-Tatlidede et al., 2012). Electrical stimulation of hippocampus has also been demonstrated to be effective and safe for controlling refractory temporal lobe epilepsy (Han et al., 2014). A recent double-blind, randomized, controlled trial in patients with refractory partial-onset seizures suggested that open loop cortical stimulation for one month resulted in a significant reduction in mean seizure frequency in the treatment group compared with that in the sham group (37.9% *versus* 17.3%) (Morrell, 2011). However, evidence that specifically supports a role of homeostatic plasticity in preventing acquired epileptogenesis or controlling epileptic seizures is still not available.

Tinnitus

Computational model predicts that appropriate additional acoustic stimulation can reverse the development of hyperactivity, which could provide a new basis for treatment strategies. In severe cases of intractable tinnitus, 37% of patients were responsive to tonic auditory cortex stimulation *via* implanted electrodes in the primary auditory cortex or overlying the secondary auditory cortex. A half of the 63% non-responders became responsive after switching to burst stimulation. The average tinnitus reduction is 53% for the entire group (De Ridder et al., 2011). Burst stimulation is capable of suppressing tinnitus in more patients more effectively than tonic stimulation, especially for noise-like tinnitus (Meng et al., 2011). The results suggest that auditory cortical stimulation may be a valuable treatment option for severe intractable tinnitus. However, non-invasive brain stimulation using repetitive transcranial magnetic stimulation (rTMS) have shown mixed results on tinnitus, with some studies showing significant improvement in the severity of

tinnitus while the others having no significant effect (Meng et al., 2011; Londero et al., 2018). Since different stimulation parameters (*i.e.*, frequency, number of stimuli per session) and study designs affect the efficacy of rTMS and treatment outcome, further basic and translational studies are needed to elucidate the efficacy and mechanism of rTMS for tinnitus.

Neuropathic pain

Motor cortical stimulation using cortical electrical stimulation or rTMS is a common treatment for refractory chronic pain including neuropathic pain and phantom pain (Lima and Fregni, 2008). Although the direct effect of high-frequency rTMS (5–20 Hz) is facilitating cortical neuronal activity, rTMS has been shown to be effective in relieving pain in refractory neuropathic pain. The underlying mechanisms of rTMS have been suggested to involve inhibition of nociceptive pathway (*e.g.*, thalamus) and the activation of pain-modulating nuclei (*e.g.*, periaqueductal gray and zona incerta) (Treister et al., 2013). Similarly, several studies demonstrated that S1 stimulation was effective in relieving pain in human and animal studies (De Ridder et al., 2007; Antal et al., 2008). We recently showed that optogenetic stimulation of layer V pyramidal neurons in S1 has analgesic effect in transient spinal cord ischemia and tibial nerve injury models of neuropathic pain and that such stimulation directly decreased S1 hyperexcitability through reducing the frequency of miniature postsynaptic current and increasing the threshold of action potential firing of these neurons in S1 (Xiong et al., 2017). These results support the idea that promoting cortical activity after somatosensory lesion will be able to control cortical hyperexcitability and reduce pain. Because the motor cortex provides strong synaptic input to the infragranular layers of S1 (Zagha et al., 2013; Kinnischtzke et al., 2014) and motor cortical stimulation suppresses evoked potentials in the S1 (Chiou et al., 2012), it is critical to understand whether motor cortical stimulation relieves chronic pain by directly inhibiting S1 activity or through a homeostatic plasticity mechanism.

Prospective

Sensory deprivation and deafferentation is traditionally used as a tool for inducing homeostatic plasticity and research on homeostatic plasticity often focuses on its physiological role and mechanism. With increasing evidence that supports a role of homeostatic plasticity in neurological conditions, further study is fundamental for establishing its role in disease mechanism and developing effective treatment strategy through activity enhancement such as cortical stimulation. The homeostatic plasticity hypothesis may also guide the development of new drugs and effective brain stimulation protocols. For example, treatment based on homeostatic plasticity would require that the frequency and pattern of cortical stimulation be similar to physiological activity and longer duration of stimulation may be more beneficial. Another approach to cortex stimulation is to combine cortex stimulation with rehabilitation or peripheral stimulation (Levy et al., 2016), which may have better effects in improving and normalizing pathway or brain activity and reducing homeostatic hyperexcitability. In tinnitus, pairing electrical stimuli and external stimuli (noise) is shown to drive cortical activity more efficiently and improve the outcome (De Ridder et al., 2014).

In conclusion, cortex stimulation is a promising approach for treating a variety of neurological disorders, but its mechanism is poorly understood. The homeostatic plasticity hypothesis may not only explain why activity stimulation can be used for treating refractory neurological diseases featuring hyperexcitability, but also provide guidance on designing protocols for cortical and brain stimulation. Such stimulation will enhance spontaneous activity and improve functional connectivity of the related network, leading to symptom relief and functional improvement. Because the activity stimulation strategy is consistent with the

intrinsic need of the body to compensate for lost function, it may be more effective and longer lasting in controlling these refractory neurological disorders.

Additional file: *Open peer review report 1*.

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Footnotes

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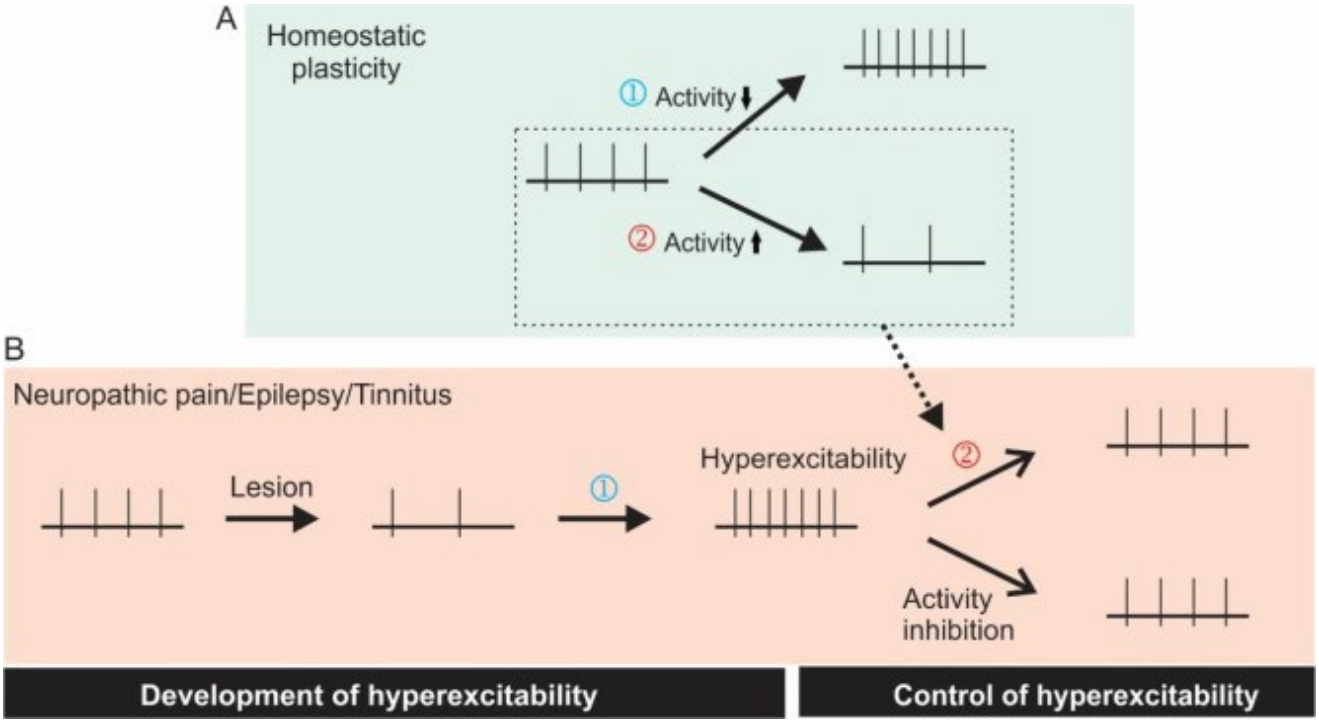
Figures and Tables

Figure 1



Two opposing strategies for controlling cortical hyperexcitability.

(A) A homeostatic plasticity mechanism suggests that activity deprivation will cause neuronal homeostatic hyperexcitability ( ) while activity enhancement reduces neuronal activity ( ). (B) Development of neuropathic pain, acquired epilepsy, and tinnitus often involves primary lesion or pathology that causes initial deprivation of afferent input or directly injury of the cortex, which may contribute to the development of hyperexcitability through a homeostatic mechanism ( ). This network hyperexcitability may be controlled either by enhancing excitatory activity so that the hyperexcitability can be reversed through the homeostatic mechanism ( ) or by directly inhibiting activity by blocking glutamate transmission or enhancing GABAergic inhibition.