J Exp Neurol. 2024;5(2):73-78.

Journal of Experimental Neurology Commentary

Homeostatic Synaptic Plasticity may be Targeted for the Prevention of Post-Stroke Epilepsy

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Received date: March 03, 2024, **Accepted date:** March 14, 2024

Citation: Adhikari Y, Jin X. Homeostatic Synaptic Plasticity may be Targeted for the Prevention of Post-Stroke Epilepsy. J Exp Neurol. 2024;5(2):73-78.

Abstract

Stroke is the most common cause of acquired epilepsy, with up to 30 percent of stroke survivors developing epilepsy over time. However, the mechanisms leading to neuronal hyperexcitability and epilepsy in stroke survivors are not fully understood. In a recently published work, we demonstrate that ischemic stroke induces homeostatic plasticity regulation in the surviving neurons in the peri-stroke area. Furthermore, activity enhancement through optogenetic stimulation of excitatory pyramidal neurons in the peri-stroke area or systemic administration of D-cycloserine, a partial N-methyl-D-aspartate (NMDA) receptor agonist, reduces seizure susceptibility in mice. Here, we briefly review current understanding on the role of homeostatic plasticity in post-stroke epileptogenesis and discuss how homeostatic plasticity could be targeted to prevent post-stroke epilepsy. We comment on our activity enhancement findings and close by discussing implications for clinical treatment.

Keywords: Post-stroke epilepsy, Ischemic stroke, Homeostatic plasticity, Two-photon imaging, Mesoscopic imaging, Activity enhancement, Optogenetics, D-cycloserine

Commentary

Stroke is characterized as a focal neurological deficit resulting from a disruption of blood flow to a specific brain region, leading to subsequent ischemia. Stroke is broadly classified as either ischemic stroke (blood flow to the brain is interrupted by an embolus or thrombus occluding a cerebral artery) or a hemorrhagic stroke (the rupture of a cerebral artery obstructs blood flow to the corresponding area of the brain). The obstruction of blood flow initiates a sequence of pathophysiological events that unfold spatially and temporally in the brain. Shortly after a stroke, oxygen-glucose deprivation in cells of the ischemic core leads to anoxic depolarization and ionic failure, ultimately resulting in necrotic cell death [1,2]. Cells in the neighboring penumbral tissue also undergo metabolic instability and functional inactivity.

Post-stroke epilepsy, defined by the International League against Epilepsy (ILAE) as "two or more unprovoked epileptic seizures occurring at least 1 week after the stroke," affects 3–30% of stroke survivors [3,4]. PSE is the most common cause of acquired epilepsy [5], accounting for about 11% of all cases of epilepsy [6,7]. It is a very significant clinical issue in stroke survivors. The prevalence of PSE varies between 2.3% to 43.0%, depending on factors such as stroke subtype (ischemic or hemorrhagic) [8,9], stroke severity [9-13] lesion location [9,14], vascular [9,15,16] and genetic factors [9,17-19]. Additionally, PSE can be influenced by CNS morbidities (early seizure, dementia, small vessel disease) and non-CNS morbidities (hypertension, peripheral infections), with mechanisms related to chronic neuroinflammation, glial scarring, angiogenesis, neurogenesis, neurodegeneration, selective neuronal loss, axonal and synaptic sprouting, and altered synaptic plasticity [19].

Homeostatic plasticity refers to the inherent ability

of neurons to "sense their own excitability and trigger negative feedback control to compensate for perturbations in synaptic activity and restrain it within a dynamic, but physiological range" [20]. This mechanism enables neural network to sustain relatively consistent firing properties over time, despite ongoing variations in electrical and synaptic characteristics [21]. In essence, homeostatic plasticity implies that neurons can perceive the level of network activity in their vicinity, generate an error signal when the neuronal activity deviates from a predetermined physiological threshold, and employ this error signal as negative feedback to adjust their excitability appropriately. This corrective action helps restore network activity to the physiological threshold. For instance, when cortical neurons experience a loss of afferent input, homeostatic plasticity mechanism may involve an increase in excitatory synaptic strength and intrinsic excitability, and/or a decrease in synaptic inhibition. These adjustments counterbalance the lost afferent input, maintaining a relatively stable level of network activity [22]. Recent *in vitro* [23-30] and *in vivo* studies also present compelling evidence supporting the implications of homeostatic plasticity mechanisms [29-31].

While homeostatic plasticity maintains a dynamic balance with Hebbian plasticity to sustain a dynamic equilibrium and ensure a stable yet flexible network activity crucial for brain function and behavior [32], accumulating evidence suggests that abnormal homeostatic regulation following acute (e.g. brain injuries) or chronic (e.g. neurodegeneration) loss of neurons/synapses may contribute to hyperexcitability [30], which could contribute to the onset of various neurological disorders. Recent investigations indicate that abnormal homeostatic regulation is implicated in epileptogenesis following brain injuries such as traumatic brain injury (TBI) or status epilepticus (SE). These injuries result in tissue damage, neuronal death, and an initial loss of activity in the surviving neurons [30,33,34]. Subsequently, homeostatic plasticity in the surviving neurons in the peri-injury area leads to an excitation scale-up (or inhibition scale-down), compensating for the lost neurons/synapses in the injured region. This process contributes to the development of hyperexcitability in the surviving neurons, thereby promoting epileptogenesis in the injured tissue.

For instance, a study by Xiong et al., demonstrated in a transient spinal cord ischemia model of neuropathic pain that there is an initial loss of activity in the cortical layer II/III pyramidal neurons of the primary somatosensory cortex within 6 hours post-injury, followed by recovery and hyperactivity within 48 hours post-injury [35]. Lower neuronal firing rates have also been reported immediately after undercut and lateral fluid percussion models of traumatic brain injuries [30,33,36]. Ping et al., has demonstrated that after a penetrating brain injury, there is an initial decrease in neuronal firing followed by an increase in neuronal firing over time [33]. These studies strongly suggest that brain injuries induce an initial loss of activity in the affected area, and subsequent homeostatic regulation during the recovery process leads to an increase in excitability over time. The heightened excitability of the neuronal network results in an imbalance between excitatory and inhibitory drive in the brain, a fundamental mechanism for seizure generation [37,38]. Compensatory homeostatic plasticity mechanisms after brain injuries can contribute to network hyperexcitability and post-traumatic epileptogenesis of the injured brain. Experimental and computational studies strongly support this concept [39-41]. In hippocampal brain slice cultures, chronic partial denervation has been shown to induce homeostatic neuronal hyperexcitability and epileptiform population spikes in the CA1 area of lesions [40]. Similarly, in a chronically isolated neocortex, hyperexcitability and focal epileptogenesis emerges through a homeostatic plasticity mechanism [39].

Recent clinical and preclinical studies support that homeostatic plasticity may also play a role in post-stroke epileptogenesis [42]. In the sub-acute stage, stroke patients exhibit suppressed ipsilateral corticomotor excitability compared to healthy patients [43-50]. On the contrary, the contralateral corticomotor excitability remains unchanged and is comparable to that of healthy adults [44,47-51], without significant alterations over time [47,48,51]. Preclinical studies further confirmed that strokes lead to a reduction in evoked potential and multi-unit activity in the peri-injury area [34,52-54]. Immediately after a stroke, low-frequency spontaneous activity is reported in the peri-injury region, followed by the emergence of high-frequency discharge, peaking 3-7 days post-stroke and sustaining high levels for up to 4 months [55-57]. In a rat middle cerebral artery occlusion model of ischemic stroke in rats, Moyanova et al. have shown that sensorimotor deficits reach their peak at 3-7 days post stroke, which is followed by a spontaneous partial recovery by days 11-14 [53].

These studies support the notion that homeostatic regulation of cortical activity may be implicated in the aftermath of a stroke. While the molecular determinants of homeostatic plasticity are not fully understood, potential factors such as alterations in receptor expression, ion gradients, phosphorylation and other modulatory factors may play a role [58-60]. In addition, post-stroke plasticity could contribute to axonal sprouting [59,61-63] and the production of dendritic spines [60,64,65], leading to a structural reorganization of the neuronal circuit. Consequently, maladaptive changes in homeostatic plasticity following a stroke could result in hyperactive and synchronized neuronal circuits, evolving into epileptic foci [66,67]. These studies support the hypothesis that neuronal homeostatic regulation may play a role in the development of post-stroke neuronal excitability and could be targeted for preventing post-stroke epilepsy.

In our recent study, we demonstrated the implication of neuronal homeostatic plasticity in the development of cortical hyperexcitability after stroke and used optogenetic and pharmacological approaches for activity enhancement

to reduce abnormal homeostatic regulation and prevent the development post-stroke hyperexcitability. The study is notable for its utilization of repeated *in vivo* two-photon imaging to assess changes in activity of individual neurons in the peri-injury area after a photothrombosis-induced ischemic stroke. *In vivo* calcium imaging of cortical layer II/III pyramidal neurons in Thy1-GCaMP6 transgenic mice revealed that ischemic stroke caused a significant decrease in calcium spike frequency, area under curve and percentage of active neurons (indicative of neuronal activity) at 3-days post-stroke. However, at 7-days post-stroke. These parameters fully recovered and were higher than that of baseline readings taken pre-stroke, suggesting that surviving neurons had become hyperexcitable after stroke. This finding is significant in that it aligns with the principles of homeostatic plasticity. Indeed, the initial loss of neuronal activity followed by the recovery of activity provides valuable insight, indicating that surviving neurons in the peri-injury area employ homeostatic regulation to scale up their excitability, attempting to compensate for the ischemia-induced loss of neighboring neurons.

These results were further substantiated by *in vivo* longitudinal mesoscopic calcium imaging of the cortex, where network activity of the neurons in the peri-injury area manifested as fluctuations in calcium fluorescence over time. At 3-days post-stroke, the area under curve of mesoscopic calcium traces was significantly lower compared to the baseline values taken pre-stroke. However, at 7-days post-stroke, the area under curve fully recovered and was significantly higher than baseline values. This initial loss of activity followed by recovery of activity further validates the findings from two-photon imaging studies. These studies were performed in 2 months old female Thy1-GCaMP6s mice. Additional studies are necessary to explore any potential age-, sex-, or strain-related effects. While these calcium imaging results provide crucial insights into the implications of homeostatic plasticity, further understanding on the neurophysiological mechanism requires electrophysiological studies of synaptic transmission and neuronal intrinsic properties.

Perhaps one of the most intriguing aspects of this study involves the use of activity enhancement to prevent homeostatic regulation in the neurons after a stroke. We employed optogenetic stimulation to selectively enhance the activity of excitatory neurons in the peri-stroke area of Thy1-ChR2-YFP transgenic mice between day 5 and day 15 post-stroke and measured its impact on seizure susceptibility 28-days post stroke. The Pentylenetetrazole (PTZ) test, which measures seizure susceptibility, revealed that mice that underwent photothrombotic stroke required lower PTZ dosage and had a shorter time latency to Racine stage V seizure (indicative of greater seizure susceptibility) compared to mice underwent sham surgery. Interestingly, mice that received activity enhancement via optogenetic stimulation after a photothrombotic stroke exhibited a lower PTZ dosage and a longer latency to seizures (indicating lesser seizure susceptibility) than those without receiving optogenetic stimulation after a stroke.

Another crucial aspect of this study involved the use of D-cycloserine, a partial N-methyl-D-aspartate (NMDA) receptor agonist that mildly enhance neuronal activity without causing post-stroke seizure, for activity enhancement to prevent homeostatic regulation after a stroke. Consistent with the results from optogenetics experiment, mice that underwent photothrombotic stroke had a lower PTZ dosage and a shorter latency (indicating greater seizure susceptibility) to PTZ induced seizures. Interestingly, activity enhancement *via* systemic administration of D-cycloserine (30 mg/kg/day) from day 5 to day 15 after photothrombotic stroke significantly increased the PTZ dosage and latency for seizure induction in mice after stroke. As a whole, these pharmacological and optogenetics studies affirm that activity enhancement can reduce abnormal homeostatic plasticity after a stroke and can be targeted to prevent post-stroke neuronal hyperexcitability. However, there are open questions to be further addressed, such as when the optimal time for activity enhancement is and whether development of post-stroke epilepsy is also prevented. It would also be intriguing to investigate whether activity enhancement will improve motor and cognitive functional recovery, in addition to the observed anti-epileptogenic effect.

Our findings also suggest that activity enhancement by DCS administration affects the excitatory and inhibitory tone in the cortex. Immunostaining against NeuN showed no difference in the density of NeuN positive mature neurons in the peri-stroke area of all groups. However, immunostaining against glutamic acid decarboxylase 67 (GAD67) revealed that DCS treatment significantly rescued the loss of cortical GABAergic interneurons in the peri-lesion region. Furthermore, immunostaining against glial fibrillary acidic protein (GFAP) showed that DCS administration significantly reduced the density of reactive astrocytes in the peri-stroke area. Overall, the result suggests a better preservation of inhibitory to excitatory drive ratio and reduced neuroinflammation in the peri-stroke area with DCS administration. However, the results leave open questions about whether other microglia and immune modulators are affected by DCS treatment and whether the given dose of DCS has any off-target effects on the uninjured contralateral cortex.

Each year, approximately 13.7 million people experience a stroke, and 5.5 million dies [68,69], making stroke the second leading cause of mortality worldwide. In the United States alone, about 795,000 people per year experience a stroke [70], accounting for approximately 1 in 19 deaths in the US. Currently thrombolytics and enzymatic therapies are available strategies for acute stroke management, which restore blood reperfusion to the affected area. While these techniques are very useful for the acute management of ischemic stroke, they only restore blood perfusion and do not target the

mechanisms of cellular injury that follow after a stroke [71]. With the availability of better medical facilities and treatment, immediate mortality due to stroke is decreasing. However, with the increase in number of stroke survivors, the number of post-stroke epilepsy patients is increasing. Unfortunately, there are no medications available that can prevent PSE development in stroke survivors. There is an urgent unmet need for therapies to prevent PSE in stroke survivors.

Our study provides important insights about the involvement of neuronal homeostatic plasticity in the development of cortical hyperexcitability after a stroke and demonstrates the efficacy of selectively enhancing the activity of excitatory neurons in the peri-stroke area on preventing the development of cortical hyperexcitability. An important finding of this paper is the identification of D-cycloserine as an activity enhancement agent. DCS, a natural product of *Streptomyces orchidaceus* and *Streptomyces garyphalus*, has already been approved by the U.S. Food and Drug Administration for human use (in tuberculosis therapy and some urinary tract infections). DCS acts at the glycine-binding site of the NMDA receptor, located at its NR1 subunit. The pharmacological profile and associated side effects of DCS in humans have already been well-characterized [72,73]. For typical antituberculosis therapy, an oral administration of 250-500 mg of DCS is used, reaching the maximum concentration (20–35 µg/mL) in the blood after 2 hours [73]. The half-life varies from 8 to 12 hours and approximately 54% to 79% of oral intake reaches the cerebrospinal fluid [74]. Currently, as many as 30 NIH funded clinical trials listed in the clinicaltrials.gov registry evaluating the efficacy of DCS on psychiatric and neurological disorders such as schizophrenia, anxiety, depression, and Alzheimer's disease [75]. Considering the fact that DCS is a safe drug, well-tolerated in human body, and is being evaluated for other diseases, DCS holds a great potential as a pharmacological agent to prevent post-stroke epilepsy by modulating homeostatic plasticity. Additionally, alternative pharmacological agents for enhancing NMDA activity, such as other selective glycine site agonists with favorable CNS bioavailability, have the potential to enhance the efficacy of this therapeutic approach and make it more appropriate for translating from bench to bedside.

Funding

This work was supported in part by the Epilepsy Research Program of the Department of Defense Congressionally Directed Medical Research Programs to XJ (Award Number: W81XWH-19-1-0543).

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