Homeostatic synaptic plasticity in the hippocampus: therapeutic prospects for seizure control?

“...it may soon be possible to selectively activate endogenous hippocampal gate keepers and molecular brakes to limit seizures or prevent epileptogenesis in those at risk.”

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The epilepsies are a class of neurological disorders characterized by the repeated occurrence of seizures [1]. Although the dysregulation of neuronal activity has been well characterized in many epilepsy disorders, the underlying causes of epileptogenesis are still unknown. In the past two decades, a class of regulatory mechanisms termed homeostatic synaptic plasticity (HSP) has been uncovered that permits neurons to establish desired ‘set points’ for neural activity and initiates compensatory responses to correct deviations from optimal levels [2,3]. We postulate that impaired homeostatic control may contribute to the etiology of certain epilepsies. Homeostatic compensations may also shed light on the refractory nature of many epilepsies to antiepileptic drug (AED) treatment. Here, we discuss recent discoveries and insights into homeostatic regulation of neural activity that show promise for guiding the development of a new generation of tools to treat epilepsy.

HSP in epilepsy: trying too hard?

The brain is highly plastic and experience-dependent changes occurring at synapses are thought to underlie normal development, learning and memory [4]. However, many popular models of synaptic plasticity (e.g., long-term potentiation) are positively reinforcing – potentiation begets even more potentiation – and are predicted to be inherently destabilizing if left unchecked [5]. HSP mechanisms stabilize neural networks by policing overall neuronal activity and adjusting synaptic strength accordingly to achieve the desired compensatory change [2]. For instance, sustained increases in network activity initiate molecular cascades that weaken excitatory and strengthen inhibitory synapses [6,7], whereas chronic decreases in activity provoke the

opposite synaptic adjustments, thus strengthening excitatory synapses while weakening inhibitory ones [6,8]. Therefore, homeostatic plasticity is thought to maintain neuronal activity within a suitable range that supports normal function.

The epilepsies can be grossly subdivided into two major categories: generalized seizures, which are thought to be predominantly genetic in origin; and partial seizures, which can arise as a consequence of focal CNS insult, such as head injury, stroke or tumors [1]. Temporal lobe structures – the hippocampus, amygdala and parahippocampal cortex – appear to be particularly vulnerable to acquired epilepsies, with mesial temporal lobe epilepsy being the most prevalent seizure condition in adults [1]. In both human and rodent models of temporal lobe epilepsy, the initial seizure episode is followed by a latent period after which spontaneous epileptiform activity emerges [9]. Following the robust neural discharges of the initial cortical insult or the ensuing status epilepticus, neural networks may experience a prolonged period of diminished network activity owing to damage (cell death, deafferentation or edema), homeostatic dampening or a combination of both. These extended periods of hypoactivity would be expected to eventually induce homeostatic restrengthening of synapses in an attempt to restore network activity. Indeed, in rodent models of hypoxia-induced neonatal seizures, compensatory hippocampal synaptic strengthening has been observed in the weeks following status epilepticus and is associated with the emergence of spontaneous seizures [10]. This observation raises the possibility that homeostatic overcompensation may underlie the emergence of spontaneous recurrent seizures. Therapeutic interventions initiated during the latent period to rescue

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the perceived network inactivity or temper the deployed homeostatic program may, therefore, alter epileptogenic processes in acquired epilepsy.

HSP in epilepsy treatment: hijacking the system

Certain treatments for epilepsy may already be commandeering endogenous homeostatic plasticity programs, albeit unknowingly. Vagus and trigeminal nerve stimulators have been shown to be effective in the treatment of epilepsy [11], although the underlying mechanisms remain unclear. Since chronic increases in network activity reliably induce homeostatic downregulation of excitatory synaptic strength [12], repeated mild stimulation of the cranial nerves may provide the slight chronic boost in excitatory drive required to activate endogenous homeostatic programs of synaptic weakening. Notably, both the vagus and trigeminal nerves project to the nucleus tractus solitarius, which in turn projects to the hippocampus, amygdala and thalamus, three areas that are heavily associated with the gating, if not the generation, of seizure activity.

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Further work is required to determine whether HSP mechanisms are, in fact, recruited in therapeutic cranial nerve stimulations. If this were the case, we would be provided with an arsenal of well-characterized molecular targets that could be developed into more sophisticated therapeutic strategies. One promising molecular target is Plk2, a protein kinase that is transcriptionally induced in response to sustained network activity and acts as a brake on excitatory synapses [12]. Inhibition of Plk2 activity has been associated with the emergence of spontaneous seizures following neonatal hypoxic seizures in rodents [10]. Intriguingly, Plk2 appears to be negatively regulated by the mTORC1 pathway [10], an intensely studied epileptogenic signaling cascade. Mutations of *TSC1* or *TSC2* upstream of mTOR cause tuberous sclerosis, in which approximately 80% of patients develop epilepsy [13]. It is therefore possible that Plk2 and attendant HSP programs provide a critical link between the etiologies of the partial (acquired) and generalized (genetic) epilepsies.

HSP in epilepsy treatment: closing the gate

An intriguing emerging view in HSP is that specific neurons, or even specific subsets of synapses,

may perform a designated role as the ‘volume control’ for neural circuits. In the hippocampus, cortical input arrives from the entorhinal cortex via two sets of pathways, the perforant path to the dentate gyrus and the temporoammonic path to CA1 [14]. Between the dentate gyrus and CA1 lies the highly interconnected CA3 auto-associative network, a powerful system of recurrent connections that allows the hippocampus to associate cortical inputs, but is also prone to generate pathological seizure activity. Inputs to the hippocampus must therefore be heavily gated to prevent runaway excitation of the CA3 network.

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Two potential avenues of therapeutic development for seizures have exploited these endogenous cell- or synapse-specific hippocampal gating mechanisms. In the first case, activity-dependent regulation of neuregulin and ErbB4 was observed following kainic acid-induced rodent seizures [15]. ErbB4 was later localized to a subtype of interneuron, which is activated by neuregulin to block seizure generation [16]. Expression of light-sensitive ion channels within this population of interneurons allows for precise optogenetic activation of the seizure ‘gate keeper’ cells [17]. In this approach, abnormal EEG activity can be used to automatically trigger light administration, thus rapidly terminating seizures in freely behaving rodents – in essence, acting as an artificially engineered homeostatic negative feedback loop [17]. This study gives researchers hope that perhaps endogenous HSP mechanisms can be harnessed to accomplish a similar result.

In the second case, we recently reported that chronic network alterations selectively alter a specific population of synapses in the hippocampus, namely the synapses between the mossy fibers of the dentate gyrus and the CA3 pyramidal neurons [18]. Mossy fiber–CA3 synapses are the largest and most powerful synapses in the brain, and may play an important role in preventing seizure generation in CA3 recurrent networks [19]. Mossy fibers activate excitatory CA3 networks as well as numerous populations of interneurons that control these networks, some of which are selectively lost in epilepsy [20]. In particular, a presynaptic mossy fiber protein, synaptoporin, was necessary and sufficient to induce homeostatic upregulation of the mossy fiber synapse, providing another potential target to limit CA3 excitation [18].

HSP & the paradox of AEDs

The most striking discrepancy between the HSP and epilepsy literature is the paradoxical effect of AEDs. Currently, the four most common clinical anticonvulsant strategies are to: inhibit action potential generation by blocking voltage-gated Na⁺ channels (e.g., phenytoin and/or carbamazepine); suppress voltage-gated Ca²⁺ channels (e.g., ethosuximide); block glutamate-gated Na⁺/K⁺/Ca²⁺ currents (e.g., felbamate and topiramate); or enhance GABA-mediated inhibition (e.g., barbiturates, benzodiazepines and clonazepam). All four strategies would be expected to decrease neuronal firing either directly or indirectly, yet when similar manipulations are chronically employed on hippocampal neurons *in vitro*, the net effect is a robust and well-characterized compensatory increase in excitatory synaptic strength on pyramidal neurons [3,6,18]. The prediction from *in vitro* studies is that, while acute administration of AEDs would act in an anticonvulsive manner, chronic administration of AEDs would ultimately increase excitatory drive and decrease inhibitory drive onto neurons, particularly once the drugs were removed – exactly the opposite of what is intended. This ‘rebound’ effect may shed

important light on the substantial population of epileptic patients (~30%) who are unresponsive to AEDs [1].

Although much work must be carried out to translate these basic findings into the clinic, it may soon be possible to selectively activate endogenous hippocampal gate keepers and molecular brakes to limit seizures or prevent epileptogenesis in those at risk. However, when it comes to tampering with delicate homeostatic balances, a subtle approach may be advised to avoid excessive overcompensation or paradoxical secondary rebound effects. In HSP, the old adage may well prove correct: less is indeed more.

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References

- Chang BS, Lowenstein DH. Epilepsy. *N. Engl. J. Med.* 349, 1257–1266 (2003).
- Turrigiano GG. The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* 135(3), 422–435 (2008).
- Queenan BN, Lee KJ, Pak DTS. Wherefore art thou, homeo(stasis)? Functional diversity in homeostatic synaptic plasticity. *Neural Plast.* 2012, Article ID 718203 (2012).
- Neves G, Cooke SF, Bliss TV. Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. *Nat. Rev. Neurosci.* 9(1), 65–75 (2008).
- Turrigiano GG, Nelson SB. Hebb and homeostasis in neuronal plasticity. *Curr. Opin. Neurobiol.* 10(3), 358–364 (2000).
- Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature* 391(6670), 892–896 (1998).
- Chang MC, Park JM, Pelkey KA *et al.* Narp regulates homeostatic scaling of excitatory synapses on parvalbumin-expressing interneurons. *Nat. Neurosci.* 13(9), 1090–1097 (2010).
- Lau CG, Murthy VN. Activity-dependent regulation of inhibition via GAD67. *J. Neurosci.* 32(25), 8521–8531 (2012).
- Dudek FE, Staley KJ. The time course of acquired epilepsy: implications for therapeutic intervention to suppress epileptogenesis. *Neurosci. Lett.* 497(3), 240–246 (2011).
- Sun H, Kosaras B, Klein PM, Jensen FE. Mammalian target of rapamycin complex 1 activation negatively regulates polo-like kinase 2-mediated homeostatic compensation following neonatal seizures. *Proc. Natl Acad. Sci. USA* 110(13), 5199–5204 (2013).
- Fisher RS. Therapeutic devices for epilepsy. *Ann. Neurol.* 71(2), 157–168 (2012).
- Pak DT, Sheng M. Targeted protein degradation and synapse remodeling by an inducible protein kinase. *Science* 302(5649), 1368–1373 (2003).
- Vezzani A. Before epilepsy unfolds: finding the epileptogenesis switch. *Nat. Med.* 18(11), 1626–1627 (2012).
- Ang CW, Carlson GC, Coulter DA. Massive and specific dysregulation of direct cortical input to the hippocampus in temporal lobe epilepsy. *J. Neurosci.* 26(46), 11850–11856 (2006).
- Eilam R, Pinkas-Kramarski R, Ratzkin BJ, Segal M, Yarden Y. Activity-dependent regulation of Neu differentiation factor/neuregulin expression in rat brain. *Proc. Natl Acad. Sci. USA* 95(4), 1888–1893 (1998).
- Tan GH, Liu YY, Hu XL, Yin DM, Mei L, Xiong ZQ. Neuregulin 1 represses limbic epileptogenesis through ErbB4 in parvalbumin-expressing interneurons. *Nat. Neurosci.* 15(2), 258–266 (2012).
- Krook-Magnuson E, Armstrong C, Oijala M, Soltesz I. On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy. *Nat. Commun.* 4, 1376 (2013).
- Lee KJ, Queenan BN, Rozeboom AM *et al.* Mossy fiber–CA3 synapses mediate homeostatic plasticity in mature hippocampal neurons. *Neuron* 77(1), 99–114 (2013).
- Lawrence JJ, McBain CJ. Interneuron diversity series: containing the detonation – feed forward inhibition in the CA3 hippocampus. *Trends Neurosci.* 26(11), 631–640 (2003).
- Sloviter RS. Decreased hippocampal inhibition and a selective loss of interneurons in experimental epilepsy. *Science* 235(4784), 73–76 (1987).