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The Widespread Network Effects of Focal Epilepsy

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Review of Sheybani et al.

Focal epilepsy is a condition in which a localized area of the brain produces spontaneous and recurrent seizures (Fisher et al., 2014). Underlying this condition is a process called epileptogenesis, which results in a seemingly normal brain becoming epileptic (Pitkanen et al., 2014). In focal epilepsy, there is a small area in the brain that has undergone epileptogenesis, which can either be congenital (e.g., resulting from genetic syndromes or focal cortical dysplasia) or acquired (e.g., resulting from infarction, tumors, or cerebral infections). This area of affected brain is predisposed to generate epileptic seizures and thus referred to as the epileptic focus. While the epileptic focus can be restricted to a small focal point in one hemisphere, seizures can generalize to the entire brain. This whole-brain generalization of the seizures demonstrates how an isolated epileptic focus can have a global cortical impact.

There is growing evidence that widespread brain dysfunction occurs in patients with focal epilepsy. For example, patients with focal epilepsy often suffer from significant and widespread neurocognitive impairments (Ung et al., 2017). Moreover, these patients appear to develop a pattern of generalized interictal epileptiform discharges or spikes that originate from sites remote from the presumed epileptic focus (Moseley et al., 2012). In addition, some patients who have undergone surgery to have the epileptic focus removed have seizures reoccur, often from sources distant to the original focus (Vaugier et al., 2018).

A recent study published by Sheybani et al. (2018) has provided insights into the generalized brain dysfunction seen in focal epilepsy. In this study, the authors used the kainate epilepsy model in which rodents were stereotaxically injected with the convulsant drug kainic acid into the left hippocampus. The kainic acid is meant to induce an epileptic focus at the site of injection. This model is thought to mimic temporal lobe epilepsy, the most common focal epilepsy seen in adult humans (Lévesque and Avoli, 2013). Using this rodent model of focal epilepsy, Sheybani et al. (2018) performed a large-scale EEG study with 32 surface electrodes and 3 intracortical electrodes. One intracortical electrode was placed in the left hippocampus, which was the site of the induced epileptic focus, another in the contralateral hippocampus, and the final one in the frontal cortex. From these many recording sites, the authors were able to identity two kinds of epileptiform activity outside of the epileptic focus. The first kind are referred to as generalized spikes, which are low-frequency interictal discharges; and the second kind are referred to as fast ripples, which are high-frequency interictal discharges. Their data demonstrate that the site from which the generalized spikes and fast ripples are generated changes with disease progression. Early in the disease, epileptiform activity is generated from the site of the kainic acid injection, the original epileptic focus. Interestingly, as the disease progresses, the authors report that generalized spikes and fast ripples are generated, not only from the epileptic focus, but also from distant sites.

The work of Sheybani et al. (2018) adds to the growing body of evidence that focal epilepsy may become a network problem as the disease progresses. Perhaps most interesting is their demonstration that the brain can generate epileptiform activity, even after the presumed epileptic focus is silenced with TTX. To explain this phenomenon, the authors hypothesize that inducing a single epileptic focus results in the development of a widespread and self-sustaining epileptic network that can become independent of the original epileptic focus. Although this certainly is a possibility, we will propose additional mechanisms that should be considered in light of the findings of Sheybani et al. (2018) that epileptiform activity can be generated outside of the epileptic focus.

First, there may be a physiological explanation for the whole-brain epilepti-

Received June 11, 2018; revised July 31, 2018; accepted Aug. 2, 2018.

This work was supported by the Mandela Rhodes Foundation and the Medical Research Council United Kingdom (for salary). We thank Dr. Joseph V. Raimondo (University of Cape Town) and Professor Andrew J. Trevelyan (Newcastle University) for thoughtful comments on this review.

The authors declare no competing financial interests.

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DOI:10.1523/JNEUROSCI.1471-18.2018

 0270-6474/18/388107-03$15.00/0

form activity described by Sheybani et al. (2018). The generalized spikes the authors describe are low-frequency events that have been shown to reflect prolonged inhibition (Gloor, 1978). Pittau et al. (2013) have suggested that this type of inhibitory or "deactivated state" is widespread in the brains of patients with focal epilepsy. In this light, generalized spikes may reflect the network's attempt to generate surround inhibition to prevent the propagation of epileptiform activity (Schwartz and Bonhoeffer, 2001; Schevon et al., 2012). Furthermore, Sheybani et al. (2018) found that generalized spikes are often accompanied by high-frequency fast ripples. Fast ripples are thought to reflect local action potential firing. Given their close association with the generalized spikes, excitatory fast ripples may be a consequence of an exaggerated inhibitory response. During generalized spikes, activation of GABA-A receptors ($GABA_AR$) may lead to an increase in intracellular chloride ($[Cl^-]_i$), causing transient depolarizing shifts in the GABA reversal potential (E_{GABA}) (Thompson and Gähwiler, 1989; Raimondo et al., 2017). Furthermore, excessive activation of the GABAergic network has been shown to result in significant elevations of extracellular potassium ($[K^+]_e$), through the K-Cl cotransporter KCC2 (Viitanen et al., 2010). This is a critical point because even slight elevations in $[K^+]_e$ result in depolarization of neuronal resting membrane potentials (Somjen, 2002). This possible combination of depolarizing $GABA_AR$ signaling and raised $[K^+]_e$ could lead to a collapse in the surround inhibition, making the network vulnerable to recruitment into seizure-like activity.

A further potential consequence of the exaggerated inhibitory response is production of a homeostatic rebound effect. Classic work by Turrigiano et al. (1994) has demonstrated that neurons have a preferred level of activity and initiate a homeostatic response to return to this preferred level after prolonged increases or decreases in activity. It is possible that persistent attempts to suppress epileptiform activity in the areas surrounding the epileptic focus eventually lead to hyperexcitability, with the neurons surpassing their homeostatic set point. In support of this idea, previous work has demonstrated that isolated neocortical tissue initially has a strongly reduced neuronal activity but becomes chronically hyperexcitable over time (Sharpless and Halpern, 1962; Sharpless, 1969). Indeed, Houweling et al. (2005) have also demonstrated that, during this period of reduced neuronal activity in isolated neocortical tissue, there is an overall increase in intrinsic excitability akin to a homeostatic response; however, this results in the production of chronic seizure-like activity.

Another hypothesis regarding the generation of epileptiform activity without contribution of the epileptic focus is provided by work from Bower et al. (2015, 2017). Their data show that epileptiform activity in humans is replayed during sleep, leading to synaptic strengthening, as has been hypothesized to underlie the consolidation of episodic memories. This might lead to the creation of neuronal ensembles comprising cells recruited either during spreading seizures or during interictal events. Consequently, aberrant epileptiform activity may become primed for recall, increasing the likelihood of more seizures. This hypothesis would take us back to the odd adage of William Gowers, that "seizures beget seizures" and result in a network disorder (Gowers, 1901; Ben-Ari et al., 2008).

Finally, the model and techniques used by Sheybani et al. (2018) may themselves lead to generalized epileptogenesis. Although the rodent kainate epilepsy model has long been used to model temporal lobe epilepsy, debate exists on whether it causes a true focal epilepsy (Lévesque and Avoli, 2013). While the injected kainic acid may remain local, the status epilepticus that follows often becomes generalized. This state of prolonged seizures following the kainic acid injection may produce widespread, albeit subtle, damage to the brain. Indeed, the induced status epilepticus may be the cause of epileptogenesis, rather than the drug. In this light, one should consider the *in vitro* work from Khalilov et al. (2003) showing that seizures induced in one hippocampus by kainic acid can lead to the formation of new epileptogenic foci in the contralateral hippocampus via the connecting commissures. Another technical issue that may have led to generalization of epileptiform activity is the authors' use of intracortical electrodes. Insertion of these electrodes may cause structural damage to the brain, leading to additional sites of epileptogenesis. It is important to keep in mind that, while one can control in these studies for the insertion of the electrodes in a saline-treated animal, this control is limited as it cannot account for the possible effects that generalized seizures have on the brain from local kainic acid injections as described above. This hypothesis is supported by the recent findings that both generalized status epilepticus and the use of preoperative intracranial recordings were associated with postoperative seizure recurrence in patients from whom the epileptic focus had been surgically removed (Mathon et al., 2017).

Nevertheless, Sheybani et al. (2018) have provided compelling data that further strengthen the argument that the effects of focal epilepsy extend beyond the initiation site. There is still much work to be done to extend our understanding of this global brain response to ictal activity to determine whether it is merely a physiological response to distal pathological activity or is itself pathological in nature. Indeed, further investigation is needed into the molecular and cellular consequences of this widespread epileptiform activity on sites far removed from the epileptic focus. Finally, it would be of significant clinical interest to match these widespread changes in network activity to the various neurocognitive and psychiatric comorbidities experienced by patients who suffer from focal epilepsy.

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