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Have You Tried Restarting It? Cortical Spreading Depression Shuts Down Seizures by Short-Circuiting Electrical Propagation

Spreading Depression as an Innate Antiseizure Mechanism

Tamim I, Chung DY, de Morais AL, Loonen IC, Qin T, Misra A, Schlunk F, Endres M, Schiff SJ, Ayata C. *Nature Communications.* 2021; 12: 2206. doi: 10.1038/s41467-021-22464-x

Spreading depression (SD) is an intense and prolonged depolarization in the central nervous systems from insect to man. It is implicated in neurological disorders such as migraine and brain injury. Here, using an in vivo mouse model of focal neocortical seizures, we show that SD may be a fundamental defense against seizures. Seizures induced by topical 4-aminopyridine, penicillin or bicuculline, or systemic kainic acid, culminated in SD at a variable rate. Greater seizure power and area of recruitment predicted SD. Once triggered, SD immediately suppressed the seizure. Optogenetic- or KCl-induced SD had a similar antiseizure effect sustained for more than 30 min. Conversely, pharmacologically inhibiting SD occurrence during a focal seizure facilitated seizure generalization. Altogether, our data indicate that seizures trigger SD, which then terminates the seizure and prevents its generalization.

Commentary

When abnormal neural activity is observed in patients or models of brain disorders, it is easy to speculate that this abnormal activity is likely to be contributing to the disease. But the brain has adapted exquisite homeostatic processes that have made it highly robust to abnormal brain activity. This makes it difficult to determine whether changes to brain activity are directly contributing to the disease state, or are actually beneficial as the brain compensates for the underlying changes that drive the disorder. In their recent article, Tamim and colleagues[1] demonstrate that an abnormal neuronal state, called spreading depression (SD), may actually be an adaptive process that disrupts seizure propagation by removing the ability of the cortex to send electrical signals. This ability to turn off electrical signaling is akin to turning off and restarting the system in local cortical circuits to break pathological chains of excitability that drive seizures.

Spreading depression is an enigmatic phenomenon where neurons completely lose their ability to send electrical signals, and the affected area slowly spreads across the cortex. This reduced activity is driven by a prolonged loss of polarization from ion gradients (i.e., spreading depolarization), which in turn leads to a prolonged depression of activity.[2,3] This SD has been linked to several neurological disorders including epilepsy, traumatic brain injury, stroke, and migraines.[4] Furthermore, this association has led to the traditional view that SD is an abnormal brain activity pattern that may be pathological and contribute to these neurological disorders.[4] However, in their recent article, Tamim and colleagues[1] present compelling evidence for an alternative view, that SD is actually a compensatory response to seizure generalization and disrupts the spread of seizures. To assess this hypothesis, the authors first characterized the relationship between chemically induced seizures and SD using *in vivo* electrophysiology after 3 distinct topical convulsants (4AP, penicillin, and bicuculline) were applied to the cortex. They found a strong positive correlation between the extent of seizure propagation and the occurrence of SD, suggesting that SD may be triggered by long-range transmission of epileptic activity. To assess the causal impact of SD on seizure propagation, the authors next evoked SD and examined how this altered the spread of the chemical-induced seizures. Incredibly, evoking SD with either potassium chloride application or with optogenetic activation strongly inhibited seizure activity and the propagation of seizures across cortex. Conversely, inhibiting SD with MK-801, an NMDA receptor blocker, increased seizure activity and propagation. Together, these experiments provide clear and compelling evidence that SD inhibits seizure activity.

While the specific mechanisms that drive SD are still poorly understood, it is clear that the loss of ion gradients (depolarization) leads to impaired signaling.[5] Because neurons communicate primarily through action potentials, which rely on resting membrane polarization, the primary outcome of SD is the complete lack of electrical signaling across large areas of the cortex. This amounts to essentially turning off parts of the cortex for many seconds to minutes, and then allowing them to reboot by repolarizing the neuronal membrane potential. In retrospect, it is actually quite predictable that blocking electrical signaling

could reduce seizure propagation, which often relies on large-scale brain networks to create pathological loops of excitation.[6] By completely removing electrical signaling from pockets of cortex, the brain is able to block these seizure networks.

This study is particularly captivating because the authors were able to assert bidirectional control over seizure propagation with direct manipulations of SD. Many studies of neurological disorders assess how the disorder alters neural activity, but few are able to provide causal evidence by directly manipulating circuit processes. This is a pervasive problem across neural circuit research, and particularly in epilepsy, as a large body of research has identified abnormal activity patterns that are *associated* with epilepsy but few activity patterns that are *causal contributors* to epilepsy. Many of these studies work on the assumption that activity patterns that correlate with seizures are likely to be pathological, rather than compensatory. In fact, many of the brain activity patterns that are associated with seizures across species have not been shown to be causal for the epileptic state. Thus, it remains possible that many of the seemingly "pathological" network properties that are observed in epilepsy (e.g., epileptic spikes[7]) may actually be beneficial for the brain to compensate for underlying changes to connectivity, excitability, or other network properties. This work by Tamim and colleagues[1] is a strong framework for testing how abnormal neural activity causally contributes to epilepsy.

An important caveat to this notion that SD is beneficial for seizure control is that there are likely major off-target effects in other brain processes that rely on electrical activity of the cortex. For instance, there are major energy demands associated with recovering from SD as the neurons need to completely repolarize across large areas of cortex. This may lead to local hypoxia and cell death within the area affected by SD, and there is some evidence that SD is associated with worse outcomes in patients with traumatic brain injury or stroke.[2,4] In addition, people with epilepsy often have major cognitive deficits that impair memory and decision-making,[8] and SD is likely to exacerbate these deficits. As the authors also point out,[1] SD appears to drive migraine headaches,[4] which can be debilitating and long-lasting, suggesting that the brain must maintain a balance between reducing seizures and limiting this highly aversive activity pattern. Thus, there is an important trade-off between the value of inhibiting seizures with SD and allowing normal brain function (with an elevated risk of seizures). This is particularly important as researchers conceive of new ways to treat seizures in people with epilepsy. The results of this study suggest that there may be natural mechanisms in the brain that can be harnessed to control seizures, but they will need to be balanced with other off-target effects that may diminish their suitability in patients. Given that the current study only examined acute seizure models, it will be important for further work to determine whether enhancing SD can improve the progression of chronic seizures and other comorbid symptoms in epilepsy.

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References

1. Tamim I, Chung DY, de Morais AL, et al. Spreading depression as an innate antiseizure mechanism. *Nat Commun*. 2021;12:2206.
2. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. *Nat Med*. 2011;17:439-447.
3. Leao AAP. Spreading depression of activity in the cerebral cortex. *J Neurophysiol*. 1944;7:359-390.
4. Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: Migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cerebr Blood Flow Metabol*. 2011;31:17-35.
5. Kraig RP, Nicholson C. Extracellular ionic variations during spreading depression. *Neuroscience*. 1978;3:1045-1059.
6. Kramer MA, Cash SS. Epilepsy as a disorder of cortical network organization. *Neuroscientist*. 2012;18:360-372.
7. Avoli M, Biagini G, de Curtis M. Do interictal spikes sustain seizures and epileptogenesis? *Epilepsy Currents*. 2006;6:203-207.
8. Kleen JK, Scott RC, Lenck-Santini PP, Holmes GL, et al., (eds). *Jasper's Basic Mechanisms of the Epilepsies*. New York: Oxford University Press, 2012.