

SEIZURES BEGET SEIZURES: A LACK OF EXPERIMENTAL EVIDENCE AND CLINICAL RELEVANCE FAILS TO DAMPEN ENTHUSIASM

Three Brief Epileptic Seizures Reduce Inhibitory Synaptic Currents, GABA_A Currents, and GABA_A-Receptor Subunits. Evans MS, Cady CJ, Disney KE, Yang L, LaGuardia JJ. *Epilepsia* 2006;47(10):1655–1664. **PURPOSE:** Cellular mechanisms activated during seizures may exacerbate epilepsy. γ -Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in brain, and we hypothesized that brief epileptic seizures may reduce GABA function. **METHODS:** We used audiogenic seizures (AGSs) in genetically epilepsy-prone rats (GEPRs) to investigate effects of seizures on GABA-mediated inhibition in the presence of epilepsy. GEPRs are uniformly susceptible to AGSs beginning at 21 postnatal days. AGSs are brief convulsions lasting 20 s, and they begin in inferior colliculus (IC). We evoked three seizures in GEPRs and compared the results with those in seizure-naive GEPRs and nonepileptic Sprague-Dawley (SD) rats, the GEPR parent strain. **RESULTS:** Whole-cell recording in IC slices showed that GABA-mediated monosynaptic inhibitory postsynaptic currents (IPSCs) were reduced 55% by three brief epileptic seizures. Whole-cell recording in IC neuronal cultures showed that currents elicited by GABA were reduced 67% by three seizures. Western blotting for the alpha1 and alpha4 subunits of the GABA_A receptor showed no statistically significant effects. In contrast, three brief epileptic seizures reduced gamma2 subunit levels by 80%. **CONCLUSIONS:** The effects of the very first seizures, in animals known to be epileptic, in an area of brain known to be critical to the seizure network, were studied. The results indicate that even brief epileptic seizures can markedly reduce IPSCs and GABA currents and alter GABA_A-receptor subunit protein levels. The cause of the reductions in IPSCs and GABA currents is likely to be altered receptor subunit composition, with reduced gamma2 levels causing reduced GABA_A-receptor sensitivity to GABA. Seizure-induced reductions in GABA-mediated inhibition could exacerbate epilepsy.

COMMENTARY

Whether “seizures beget seizures” has been a point of contention ever since Sir William Gowers coined this aphorism more than 125 years ago (1). Although there is convincing experimental evidence to support this premise, current understanding suggests that it is not clinically applicable and that, with the exception of some rare syndromes, human epilepsy is not a progressive, self-perpetuating disorder (2). Potentially clouding this knowledge is the increasing recognition that early life episodes of complex febrile seizures are associated with the later development of temporal lobe epilepsy (3) and that the number of pretreatment seizures is related to the probability of subsequent remission (4). These findings are, of course, entirely separate issues from the suggestion that one seizure increases the likelihood of another.

Unfortunately, the boundaries of these phenomena have become somewhat blurred amid the recent clamor to investigate the cellular mechanisms of epileptogenesis and to assess how these mechanisms might be exploited to prevent or delay the development of epilepsy (5). The procedure of employing

acute experimental seizures as a precipitant of a subsequent epileptic state and dissecting the myriad of molecular events that occur in the latent period is a perfectly reasonable and legitimate endeavor. However, a troubling departure from this effort has involved a regression to Gowers’s dictum and resulted in a largely unwritten acceptance of the theory that a single seizure or cluster of seizures can predispose to further episodes. In their enthusiasm preclinical investigators can, on occasion, lose sight of the importance of clinical relevance and, more specifically, the fact that epileptogenesis, pharmacoresistance, and seizures begetting seizures are not one and the same thing.

The recent manuscript by Evans et al. examined the effect of three successive audiogenic seizures on the GABA neurotransmitter system in the inferior colliculus of the genetically epilepsy-prone rat (GEPR). Twenty-four hours after the final seizure, the investigators observed a pattern of cellular effects that was consistent with an alteration in the subunit composition of the postsynaptic GABA_A receptor, leading to a decrease in its sensitivity to GABA and an attenuation of inhibitory neurotransmission in the site of seizure origin. They deduced that compromised GABAergic inhibition in the inferior colliculus could predispose to further seizures and contribute to the phenomenon of audiogenic kindling (6–8). This has, after all, been mooted as one of the principal mechanisms of seizure susceptibility in the GEPR (9). However, the authors chose

not to comment on the apparent hyperactivity of GABAergic inhibition in the inferior colliculus of seizure-naïve, epilepsy-prone rats, when compared to nonepileptic control animals. Arguably, this is a more intriguing finding—one that may underlie the epileptogenic nature of the aforementioned diminution in GABAergic activity, and one that certainly has a significant bearing on how this study could or should be interpreted. Instead, the authors elected to focus on clinical relevance, suggesting that their study might explain the phenomenon of seizure clustering and have implications for epileptogenesis, pharmacological responsiveness, and the treatment of epilepsy after a single unprovoked seizure.

At this stage, the margins of disparate clinical issues begin to merge and interpretation becomes a little questionable. On the surface, these investigators have succeeded in identifying a mechanism by which seizures *might* beget seizures, at least in the GEPR. However, it is not appropriate to then extrapolate this observation to the clinical arena where the phenomenon does not exist or attempt to align it with any other vaguely related clinical circumstance. There is no doubt that the study provides a novel insight into the cellular consequences of audiogenic stimulation in the GEPR, but it also offers up more questions than answers. The permanence of the observed effects and how they relate to the number and/or frequency of seizures is not addressed, and the authors fail to discount the possibility that repeated exposure to intense audiogenic provocation might elicit similar changes in the inferior colliculus of normal animals, particularly as this structure represents the primary point of convergence for multiple, bilateral auditory afferents (10). Finally, they provide no direct experimental evidence that would support their proposed exacerbation of seizures. Demonstrating that seizure severity increased with successive stimulations would have added a behavioral correlate to the cellular and molecular findings and offered at least some support to the principal findings of this manuscript.

Despite the authors' assertions to the contrary, there is little in their paper to confirm that repeated seizures are associated with enhanced epileptogenicity in the GEPR and nothing to suggest that these findings have any relevance to the exacerbation of clinical epilepsy. This investigation has elegantly demonstrated the effect of a single seizure or a brief cluster of

seizures on GABA-mediated inhibition in the primary epileptogenic zone in the GEPR but any interpretation of the findings should end there. In one sense, the conclusions of this paper are a little misguided, possibly as a result of ongoing efforts to unravel the phenomena of epileptogenesis, pharmacoresistance, and self-perpetuating seizures. In another sense, however, they are in keeping with an increasing extravagance in contemporary scientific reporting. Seizures may not beget seizures but research trends can, on occasion, beget overinterpretation of results.

by Graeme J. Sills, PhD

References

1. Gowers WR. Epilepsy and other chronic convulsive disorders: their causes, symptoms and treatment. London: J&A Churchill, 1881.
2. Berg AT, Shinnar S. Do seizures beget seizures? An assessment of the clinical evidence in humans. *J Clin Neurophysiol* 1997;14:102–110.
3. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. *N Engl J Med* 1987;316:493–498.
4. Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. *Eur J Neurol* 2006;13:277–282.
5. Walker MC, White HS, Sander JWAS. Disease modification in partial epilepsy. *Brain* 2002;125:1937–1950.
6. Naritoku DK, Mecozzi LB, Aiello MT, Faingold CL. Repetition of audiogenic seizures in genetically epilepsy-prone rats induces cortical epileptiform activity and additional seizure behaviors. *Exp Neurol* 1992;115:317–324.
7. N'Gouemo P, Faingold CL. Repetitive audiogenic seizures cause an increased acoustic response in inferior colliculus neurons and additional convulsive behaviors in the genetically-epilepsy prone rat. *Brain Res* 1996;710:92–96.
8. N'Gouemo P, Faingold CL. Audiogenic kindling increases neuronal responses to acoustic stimuli in neurons of the medial geniculate body of the genetically epilepsy-prone rat. *Brain Res* 1997;761:217–224.
9. Faingold CL. Role of GABA abnormalities in the inferior colliculus pathophysiology—audiogenic seizures. *Hearing Res* 2002;168:223–237.
10. Malmierca MS. The inferior colliculus: a center for convergence of ascending and descending auditory information. *Neuroembryol Aging* 2004;3:215–229.