Too Much Inhibition Leads to Excitation in Absence Epilepsy

Enhanced Tonic $GABA_A$ Inhibition in Typical Absence Epilepsy. Cope DW, Di Giovanni G, Fyson SJ, Orbán G, Errington AC, Lorincz ML, Gould TM, Carter DA, Crunelli V. *Nat Med* 2009;(12):1392–1398. The cellular mechanisms underlying typical absence seizures, which characterize various idiopathic generalized epilepsies, are not fully understood, but impaired γ-aminobutyric acid (GABA)-ergic inhibition remains an attractive hypothesis. In contrast, we show here that extrasynaptic $GABA_A$ receptor–dependent 'tonic' inhibition is increased in thalamocortical neurons from diverse genetic and pharmacological models of absence seizures. Increased tonic inhibition is due to compromised GABA uptake by the GABA transporter GAT-1 in the genetic models tested, and GAT-1 is crucial in governing seizure genesis. Extrasynaptic $GABA_A$ receptors are a requirement for seizures in two of the best characterized models of absence epilepsy, and the selective activation of thalamic extrasynaptic $GABA_A$ receptors is sufficient to elicit both electrographic and behavioral correlates of seizures in normal rats. These results identify an apparently common cellular pathology in typical absence seizures that may have epileptogenic importance and highlight potential therapeutic targets for the treatment of absence epilepsy.

COMMENTARY

A fundamental principle of the pathophysiology of epilepsy is that seizures result from an imbalance in the normal excitatory and inhibitory mechanisms controlling electrical excitability in the brain. While a large number of neurotransmitters, ion channels, and other molecules regulate neuronal excitability, abnormalities in GABA, the major inhibitory neurotransmitter of the brain, perhaps represent the mechanism that is most frequently implicated in epilepsy. In particular, a deficiency or loss of GABA inhibition is hypothesized to be pathogenic in a variety of genetic and acquired epilepsies (1,2). Conversely, drugs that enhance GABA function, such as benzodiazepines, phenobarbital, and vigabatrin, represent effective treatments for essentially all types of seizures.

While a decrease in GABAergic inhibition should intuitively be expected to be proepileptogenic, enhanced GABAergic inhibition has also been observed in a number of models of epilepsy (3–6). In this context, increased GABAergic inhibition may predominantly represent a compensatory response of the brain in an attempt to decrease seizure propensity. However, enhanced GABA inhibition has been reported paradoxically to *promote* seizures as well, at least in some specific types of epilepsy models (6). Furthermore, GABA agonist drugs can exacerbate seizures in limited circumstances (7). Thus, GABAergic inhibition potentially may be proepileptogenic as well as antiepileptogenic, but the frequency and specific mechanisms of the paradoxical excitatory effects of GABA inhibition are poorly understood.

The recent study by Cope et al. provides novel evidence that enhanced GABAergic inhibition may actually represent a relatively common pathophysiological phenomenon that contributes to the genesis of one of the most common forms of epilepsy: absence epilepsy. Typical absence seizures are the cardinal seizure type of several prototypic idiopathic generalized epilepsies. The anatomical basis of absence seizures is relatively well delineated and likely involves thalamocortical networks that also generate normal physiological oscillations, such as sleep spindles (8). In particular, thalamocortical relay neurons project excitatory inputs to cortical pyramidal cells, which send reciprocal excitatory projections back to the same thalamic nuclei. In addition, GABAergic interneurons, such as in the reticular nucleus of the thalamus, inhibit thalamocortical relay neurons and help generate and pace oscillations of alternating excitation and inhibition throughout this network. It is commonly assumed that the generalized spike-and-wave discharges of absence seizures represent a pathological exaggeration of normal spindle-like oscillations originating from these same thalamocortical networks (8). However, the specific cellular mechanisms by which absence seizures are produced are still incompletely understood, including the extent of involvement of GABAergic signaling.

GABA-mediated inhibition could influence absence seizures through several different mechanisms. Synaptic $GABA_A$ receptors mediate inhibitory postsynaptic potentials involved in conventional fast inhibitory synaptic transmission (i.e., phasic inhibition). By comparison, extrasynaptic $GABA_A$ receptors respond to ambient GABA to cause tonic inhibition, which may be persistently active at a low basal level. In addition, $GABA_B$ receptors, which unlike $GABA_A$ receptors do not contain an intrinsic ion channel, may regulate other receptors and channels by activation of second messengers. The study by Cope et al. reports the surprising finding that GABAergic signaling in absence epilepsy is abnormal and involves a consistent enhancement of extrasynaptic tonic $GABA_A$ inhibition.

This study by Cope and colleagues impressively demonstrates the basic finding of enhanced tonic GABA inhibition of

Epilepsy Currents, Vol. 10, No. 5 (September/October) 2010 pp. 131–133
Wiley Periodicals, Inc.

thalamocortical neurons in a diverse variety of both established and new animal models of absence seizures. The findings include several genetic models of spontaneous absence epilepsy, such as the genetic absence epilepsy rats from Strasbourg (GAERS), the stargazer and lethargic mutant mice, as well as pharmacological models of acutely induced absence seizures and generalized spike-and-wave discharges in rodents administered GABA modulating drugs, such as γ-hydroxybutyric acid (GHB) and 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridine-3-ol (THIP). Only one out of eight models (i.e., the tottering mutant mice) of absence seizures examined did not show evidence of exaggerated GABA inhibition, and in this one model, the control nonmutant background strain already had elevated GABA inhibition. Using pharmacological and electrophysiological techniques, the authors provide evidence that the enhanced GABAergic signaling in these models is selective for extrasynaptic tonic inhibition and that conventional fast $GABA_A$ inhibitory synaptic transmission is relatively unaffected. Furthermore, as THIP at low concentrations is selective for extrasynaptic $GABA_A$ receptors, the fact that they were able to demonstrate that local intrathalamic administration of THIP induces absence seizures is further indication that enhanced tonic GABA inhibition in thalamic circuits is sufficient to cause absence seizures. Conversely, knock down of extrasynaptic $GABA_A$ receptors by genetic methods reduced tonic inhibition and prevented induced absence seizures in the GHB model and spontaneous absence seizures in the GAERs model, suggesting that the enhanced extrasynaptic tonic inhibition is necessary to cause absence seizures.

In addition to demonstrating that enhanced tonic inhibition in thalamus is a common finding that is necessary and sufficient to generate absence seizures, the Cope et al. study also provides evidence for a possible mechanism causing the increased GABAergic inhibition. Ambient, basal levels of extrasynaptic GABA are kept relatively constant by a balance between release and diffusion of synaptic GABA from neurons and reuptake by GABA transporters of neurons and glia. Using pharmacological and genetic methods, the study found that GABA uptake by a specific GABA transporter, GAT-1, is compromised in a couple of the genetic models of absence epilepsy (i.e., GAERS, stargazer) and that GAT-1 knock-out mice display enhanced GABAergic inhibition in thalamus and spontaneous absence seizures. Overall, the authors propose that elevated extracellular GABA levels caused by deficient GAT-1 activity lead to enhanced tonic $GABA_A$ inhibition and persistent hyperpolarization of thalamocortical relay neurons, effectively shunting or gating information flow through the thalamus and potentially accounting for behavioral arrest and unresponsiveness during absence seizures.

Given the robust and consistent findings in multiple animal models, this study is significant in identifying a novel, somewhat paradoxical, mechanism of absence seizures. However, there are critical issues relating to the role of enhanced tonic inhibition in absence epilepsy that remain unexplained. First, the origin of the observed GAT-1 defect is not clear, as GAT-1–expression levels were normal in the GAERS model. While abnormal expression or function of GABA transporters has also been reported in nonabsence seizure models (9,10), it is likely that mechanisms other than GAT-1 contribute to enhanced tonic GABA inhibition in absence epilepsy, although no evidence was found for several alternative mechanisms in this study. Second, how the enhanced tonic inhibition actually influences the behavior of thalamocortical circuits to promote spike-and-wave discharges and to foster the clinical manifestations of absence seizures was not specifically addressed in this study. While the authors speculate that persistent hyperpolarization of thalamocortical neurons should interrupt information flow through the thalamus, this does not necessarily account for the oscillatory behavior of these circuits in generating spike-and-wave discharges that are presumably central to absence seizures. Future studies are needed to determine how too much inhibition promotes excitation in absence epilepsy.

by Michael Wong, MD, PhD

References

1. Treiman DM. GABAergic mechanisms in epilepsy. *Epilepsia* 2001;42(suppl 3):8–12.
2. Galanpoulou AS. Mutations affecting GABAergic signaling in seizures and epilepsy. *Pflugers Arch* 2010;40:505–523.
3. Zhan RZ, Nadler JV. Enhanced tonic GABA current in normotopic and hilar ectopic dentate granule cells after pilocarpine-induced status epilepticus. *J Neurophysiol* 2009;102:670–681.
4. Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. *J Neurosci* 2005;25:7724–7733.
5. Scimemi A, Semyanov A, Sperk G, Kullmann DM, Walker MC. Multiple and plastic receptors mediate tonic GABAA receptor currents in the hippocampus. *J Neurosci* 2005;25:10016–10024.
6. Klaasen A, Glykys J, Maguire J, Labarca C, Mody I, Boulter J. Seizures and enhanced cortical GABAergic inhibition in two mouse models of human autosomal dominant nocturnal frontal lobe epilepsy. *Proc Natl Acad Sci USA* 2006;103:19152–19157.
7. Hosford DA, Wang Y. Utility of lethargic (lh/lh) mouse model of absence seizures in predicting the effects of lamotrigine, vigabatrin, tiagabine, gabapentin, and topiramate against human absence seizures. *Epilepsia* 1997;38:408–414.
8. Beenhakker MP, Huguenard JR. Neurons that fire together also conspire together: Is normal sleep circuitry hijacked to generate epilepsy? *Neuron* 2009;62:612–632.
9. During MJ, Ryder KM, Spencer DD. Hippocampal GABA transporter function in temporal lobe epilepsy. *Nature* 1995;376:174–177.
10. Patrylo PR, Spencer DD, Williamson A. GABA uptake and heterotransport are impaired in the dentate gyrus of epileptic rats and humans with temporal lobe sclerosis. *J Neurophysiol* 2001;85:1533–1542.