Arresting a Seizure by Dropping a Little Acid

Seizure Termination by Acidosis Depends on ASIC1a. Ziemann AE, Schnizler MK, Albert GW, Severson MA, Howard MA 3rd, Welsh MJ, Wemmie JA. *Nat Neurosci* 2008;11(7):816–822. Most seizures stop spontaneously; however, the molecular mechanisms that terminate seizures remain unknown. Observations that seizures reduced brain pH and that acidosis inhibited seizures indicate that acidosis halts epileptic activity. Because acid-sensing ion channel 1a (ASIC1a) is exquisitely sensitive to extracellular pH and regulates neuron excitability, we hypothesized that acidosis might activate ASIC1a, which would terminate seizures. Disrupting mouse ASIC1a increased the severity of chemoconvulsant-induced seizures, whereas overexpressing ASIC1a had the opposite effect. ASIC1a did not affect seizure threshold or onset, but shortened seizure duration and prevented seizure progression. CO_2 inhalation, long known to lower brain pH and inhibit seizures, required ASIC1a to interrupt tonic-clonic seizures. Acidosis activated inhibitory interneurons through ASIC1a, suggesting that ASIC1a might limit seizures by increasing inhibitory tone. Our results identify ASIC1a as an important element in seizure termination when brain pH falls and suggest both a molecular mechanism for how the brain stops seizures and new therapeutic strategies.

COMMENTARY

It is well known that the vast majority of seizures terminate spontaneously, but the underlying mechanisms responsible for such cessation are unclear. GABAergic mechanisms primarily have been invoked for the generalized inhibition that follows cellular and network hyperexcitability witnessed at both cellular and electroencephalographic levels (1); however, endogenous adenosine release and actions on purinergic receptors have been implicated as well (2). One intriguing line of speculation involves modulation of ion channels by protons—a notion supported by long-standing historical observations that neuronal activity and seizures can reduce brain pH (3) and that hypercarbic acidosis can inhibit epileptiform discharges in both patients with epilepsy and rodents (4,5).

Ion channels that can be modulated by protons include NMDA and AMPA receptors (6), $GABA_A$ receptors (7), voltage-gated sodium and calcium channels (8), as well as the KCNQ family of voltage-gated potassium channels (9). It is important to note that these channels are the principal molecular targets of most clinically effective anticonvulsant medications. Under conditions of lowered extracellular pH, proton modulation of these important ion channels would undoubtedly affect neuronal excitability.

Along similar lines, investigators have described an unusual family of proton-gated ion channels exhibiting sodium and calcium conductances over a range of pH values, which have been reported in both animals and humans undergoing seizure activity (10). Acid-sensing ion channels (so-called, ASICs) have been identified in seizure-prone brain regions, such as the hippocampus and neocortex (11). Interestingly, inhibitory interneurons appear to display more prominent proton-gated currents than excitatory neurons (12). Collectively, these observations suggest that increased activity of ASICs might preferentially depolarize interneurons in a manner such that overall inhibitory tone is increased; and, under conditions of enhanced neuronal excitability and synchrony, this action could block propagation of epileptiform discharge.

It is in this context that Ziemann and colleagues asked whether the presence or absence of ASIC1a might influence electroclinical seizures induced by chemoconvulsants. They found that the targeted deletion of the murine *Asic1a* gene results in an attenuation of seizure severity in response to the excitotoxin kainate and the $GABA_A$-receptor antagonist pentylenetetrazol. While seizure duration and progression were diminished in *Asic1a* knockout mice, neither seizure threshold nor onset was affected. Additionally, the extent of postictal depression was reduced in *Asic1a*-null mutants. No effects were seen during the first 10 minutes of seizure activity. This timeframe is intriguing because it is now understood that the critical transition from brief recurrent seizures to status epilepticus may be in the neighborhood of a 10-minute time point (13,14).

Given the broad distribution of ASIC1a on pyramidal cells and interneurons in the brain, Ziemann and colleagues then sought further evidence that this proton-gated channel might inhibit seizure activity through a preferential action on inhibitory interneurons. In the low magnesium model of epileptiform activity, they found that when the pH was lowered to 6.8, seizure activity decreased in wild-type hippocampal slices but not in slices from *Asic1a* knockout mice. Next, they demonstrated that acutely dissociated hippocampal inhibitory interneurons exhibited more prominent acid-evoked currents compared with excitatory pyramidal neurons in the wild-type slices. In contrast to the robust acid-evoked action potential discharge in wild-type interneurons, lowered extracellular pH failed to evoke firing in interneurons from *Asic1a*-null mice. Finally, using a fiber optic pH sensor, these investigators demonstrated that brain pH dropped in vivo during pentylenetetrazol-evoked seizures and in response to CO_2

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inhalation, although CO_2 had little effect in *Asic1a* knockout mice.

Taken together, the results of Ziemann and colleagues strongly support the view that ASIC1a plays a very important role in seizure termination and postictal depression. ASIC1a may very well determine, in part, whether a brief spontaneous seizure transitions into status epilepticus. However, due to the 10-minute latency to a putative ASIC1a-mediated effect, other mechanisms (such as those cited above) may be equally or more important for the spontaneous cessation seen with most epileptic seizures.

This novel study raises a number of interesting questions. 1) Could some patients who frequently go into status epilepticus have underlying defects in ASIC1a? 2) Does this study bear any relevance to the mechanism of action of certain anticonvulsant medications, such as acetazolamide, topiramate, and zonisamide, that inhibit carbonic anhydrase enzymes? 3) Could ASIC1a be involved in the mechanism of action of the ketogenic diet (KD), a nonpharmacological therapy for medically refractory epilepsy, characterized by ketoacidosis? Available evidence suggests that the brain pH is unaltered by the KD (although whether or not there are significant pH changes in microdomains or around specific cell types remains unknown) (15). 4) It is well known that hyperventilation, resulting in hypocarbia, can provoke generalized absence seizures. Does ASIC1a contribute to generalized spike-wave discharges or even normal thalamocortical rhythms? 5) What does the present study imply about the role of pH in the control of experimental febrile seizures? Schuchmann and colleagues observed that hyperthermia induces respiratory alkalosis in the immature brain and precipitates seizure activity, which can be quickly suppressed with ambient CO_2 (16).

There are important treatment implications to consider as well. Can safe pharmacological agents be developed to activate ASIC1a, and can such agents be cell-type specific, preferentially activating ASICs on inhibitory interneurons? Could ASIC1a-mediated activation of interneurons actually increase network activity and synchrony, potentially exacerbating seizure activity? If patients with epilepsy have significant loss of interneurons, would ASIC1a-mediated activation of excitatory pyramidal neurons also result in hyperexcitability? Notwithstanding these considerations, could ASIC activators constitute a new class of compounds for the treatment of status epilepticus, potentially obviating the limitations of GABAergic agents that fail in the treatment of prolonged seizures due to $GABA_A$-receptor desensitization and internalization? Finally, could hypercarbia, simply administered through facemasks, be an effective adjunctive interventional strategy for recurrent and prolonged seizures? In the end, ASIC1a is likely only one factor that limits excitability during seizure activity, with other mechanisms influencing seizure threshold and onset and contributing to seizure cessation and postictal depression. While there remain many outstanding questions and implications posed by the study by Ziemann et al., this stimulating investigation establishes a novel molecular target for therapeutic intervention. Truly, "dropping a little extracellular acid" may prove to be an "arresting" phenomenon.

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