The Wanderer Falters: Central Vagal Dysregulation Triggers SUDEP

Spreading Depolarization in the Brainstem Mediates Sudden Cardiorespiratory Arrest in Mouse SUDEP Models.

Aiba I, Noebels JL. *Sci Transl Med* 2015;7(282):282ra46.

Cardiorespiratory collapse after a seizure is the leading cause of sudden unexpected death in epilepsy (SUDEP) in young persons, but why only certain individuals are at risk is unknown. To identify a mechanism for this lethal cardiorespiratory failure, we examined whether genes linked to increased SUDEP risk lower the threshold for spreading depolarization (SD), a self-propagating depolarizing wave that silences neuronal networks. Mice carrying mutations in Kv1.1 potassium channels (–/–) and *Scn1a* sodium ion channels (+/R1407X) phenocopy many aspects of human SUDEP. In mutant, but not wild-type mice, seizures initiated by topical application of 4-aminopyridine to the cortex led to a slow, negative DC potential shift recorded in the dorsal medulla, a brainstem region that controls cardiorespiratory pace-making. This irreversible event slowly depolarized cells and inactivated synaptic activity, producing cardiorespiratory arrest. Local initiation of SD in this region by potassium chloride microinjection also elicited electroencephalographic suppression, apnea, bradycardia, and asystole, similar to the events seen in monitored human SUDEP. In vitro study of brainstem slices confirmed that mutant mice had a lower threshold for SD elicited by metabolic substrate depletion and that immature mice were at greater risk than adults. Deletion of the gene encoding tau, which prolongs life in these mutants, also restored the normal SD threshold in Kv1.1-mutant mouse brainstem. Thus, brainstem SD may be a critical threshold event linking seizures and SUDEP.

Commentary

“Cardiorespiratory collapse” is an ominously descriptive moniker, but no more so than the expression used to describe what is arguably the most frightening aspect of uncontrolled epilepsy: sudden unexpected (or unexplained) death in epilepsy (SUDEP). For epilepsy patients, especially those with uncontrolled seizures, the threat of sudden, unexpected death is more than 20-fold higher than in the general population, and SUDEP is the leading cause of death in some patient groups. Since SUDEP is, by definition, unpredictable and unexplained, it is imperative to elucidate its underlying mechanisms. Based on retrospective studies, risk factors for SUDEP are many, but the hypothesis that dysregulation of brain regions controlling cardiac functions, respiratory functions, or both has gained traction in recent studies aimed at identifying the underlying causes of SUDEP. Individuals with epilepsy display autonomic abnormalities, including ictal tachycardia or bradycardia, cardiac arrhythmias, blood oxygen desaturation, and apnea, implicating seizure-associated central autonomic dysfunction as a contributor to SUDEP. Similar outcomes have also been identified in rodent models of epilepsy, particularly epilepsies of genetic etiology, prompting Aiba and Noebels to investi-

gate whether physiological abnormalities in the dorsal brainstem accompany seizures and SUDEP resulting from cardiorespiratory collapse in two genetic models of epilepsy. In both mouse lines studied (i.e., Kv1.1 knock-out and Nav1.1 deficient “Dravet” mice), spontaneous seizures and susceptibility to SUDEP are expressed within weeks after birth, representing translationally relevant models of SUDEP in genetic epilepsies.

Seizure activity impinges on brainstem autonomic neurons that control cardiorespiratory responses, independent of peripheral influences (1), consistent with a central autonomic contribution to SUDEP etiology. While recording respiration and electrical signals in the heart, neocortex, and dorsal brainstem, Aiba and Noebels found that focal cortical seizures evoked in Kv1.1 knock-out mice resulted in apnea, bradycardia, cardiac arrhythmias, flattening of the cortical EEG, and death. They also recorded electrical activity in the dorsal brainstem, including the nucleus tractus solitarius (NTS), an area that receives primary viscerosensory autonomic input and mediates baroreceptor and cardiorespiratory reflexes. A direct current shift representing spreading depolarization (SD) in the dorsal brainstem of Kv1.1 knock-out mice coincided with cardiorespiratory collapse and cortical EEG suppression and always preceded death after focal cortical seizures. In neural networks, SD represents an intrinsically propagating membrane depolarization that renders neurons incapable of firing action potentials—essentially shutting down neural activity in the system. The occurrence of SD in the brainstem

after cortical seizure was not observed in control mice, but the effect was reproduced in the Dravet mouse, implicating the collapse of neuronal signaling integrity in the NTS as a trigger for SUDEP.

The authors also induced SD in the brainstem of control and Kv1.1 mice, which led to apnea and bradycardia and suppression of the cortical EEG. Seizures can deplete ATP levels, compromising brain energy metabolism. Depriving brainstem slices from juvenile Kv1.1 and Dravet mice of both oxygen and glucose resulted in lower SD threshold than in control mice, an effect that was moderated by increasing glucose concentration and affected by K^+ channel or NMDA-receptor blockade in a manner consistent with the hypothesis that increased neuronal excitability owing to reduced K^+ channel function in Kv1.1 knock-out mice contributes to SD. Mechanisms explaining the threshold difference in slices from Dravet mice, however, are not as straightforward. Notably, because the NTS—especially the lateral NTS from which the SD originated—is densely populated with GABAergic interneurons (2), reduced Na^+ channel function in the Dravet mice could imply a role for reduced synaptic inhibition in the development of SD. The transition from increased neuronal excitability to SD, especially with metabolic depletion, is marked by a dramatic and abrupt breakdown of ionic gradients across the membrane in a group of neurons. This results in a cascade of events that includes release of ions and neurotransmitters locally, which can in turn affect neighboring cells (3). The brainstem is relatively resistant to SD normally (4), but an increase in NTS neuron excitability combined with metabolic deprivation might contribute to the decreased threshold for SD development in the NTS of seizure-prone mice. The take-home message is that a reduction in the SD threshold in the vagal complex appears to be a critical factor underlying seizure-related cardiorespiratory collapse and death.

The findings of Aiba and Noebels show, for the first time, a direct link between seizures, increased susceptibility to SD in the dorsal brainstem, and consequent failure of central autonomic cardiorespiratory regulation. Rather than focusing on the debate over whether SUDEP is due to the failure of cardiac, respiratory, or a combination of systems, the authors present evidence that failure of the coordinating brainstem center (i.e., the NTS) responsible for regulating these vital physiological functions underlies SUDEP, representing a paradigm shift that could lead to preventative treatments or biomarkers for this devastating outcome. The work by Aiba and Noebels suggests that altered ion-channel function in mutant mice is sufficient to precipitate both seizure development and SUDEP. But, in both models assessed, development of spontaneous seizures is accompanied by many of the cellular changes associated with other, nongenetic epilepsies (e.g., mossy fiber sprouting, synaptic reorganization). These cellular changes, along with spontaneous seizure development, are abrogated by genetic deletion of the microtubule-associated protein, tau (5). Consistent with the attenuation of epileptogenesis, Aiba and

Noebels found that *tau* deletion in Kv1.1 mice normalized the SD threshold in the NTS. Rather than being a direct function of a channel mutation, it seems possible that additional factors associated with epileptogenesis contribute to the lower SD threshold in the NTS. These factors remain undescribed, and the specific cellular pathophysiology in the NTS leading to increased likelihood of SD development is unknown. Although prevalent in patients with specific mutations leading to genetic epilepsies, SUDEP occurs frequently in cases where no underlying genetic abnormality has been identified, including in acquired epilepsies, which account for the plurality of epilepsy types in patients. Determining if SD in the vagal complex is associated with SUDEP in other types of epilepsy is imperative.

Fundamental aspects of NTS neurobiology may hold the keys to discovering how epilepsy modifies the physiology of the system. For example, vagal viscerosensory afferents make an obligatory synapse in the NTS, and vagal stimulation is used therapeutically for some otherwise intractable epilepsies. Like many cortical circuits, central vagal circuitry is highly plastic, being substantially modified by fluctuations in synaptic drive (6, 7). Unlike most brain areas, the NTS contains fenestrated capillaries and is therefore outside the blood–brain barrier (8), offering a target for pharmacologic interventions that may not otherwise affect brain function. Identifying the effects of epileptogenesis in central autonomic control areas may prompt the development of preventative therapies for SUDEP, which would be welcome relief for patients and their families.

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