Editorial

Misplaced Brain Sodium Channels in Heart Kindle Sudden Death in Epilepsy

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Sudden unexplained death in epilepsy (SUDEP) is responsible for ≈2000 deaths per year in the United States and accounts for ≤15% of all epilepsy-associated mortality by most recent estimates.[1,2] Risk of SUDEP is greatest in persons with treatment-refractory epilepsy. The cause of death in SUDEP is cardiorespiratory arrest, but there is uncertainty whether cardiac arrhythmia (tachycardia or bradycardia) or respiratory arrest is the primary mechanism. Ascertaining the predominant cause of death in SUDEP will offer opportunities to implement preventive measures to preserve life in persons with epilepsy.

Article see p 912

Cardiac arrhythmia is the dominant cause of sudden unexplained death in the general adult population and early investigations of SUDEP focused on this mechanism. During seizures (ictal phase), abnormal heart rhythms (mostly tachycardia, presumed sinus in origin) and various electrocardiographic changes have been observed. Bradycardia and asystole are commonly observed in the postictal period when abnormal respiration and accompanying hypoxemia are prevalent.[1] By contrast, ventricular tachyarrhythmia has been associated with seizures less frequently[3] and typically occurs in the setting of pre-existing heart disease.[4,5] However, periictal abnormalities in myocardial repolarization (QTc interval lengthening or shortening, increased QT dispersion), which are well-established risk factors for life-threatening ventricular arrhythmia in the general population, have been reported in some epilepsy cases series,[6–9] but not all.[10] Moreover, treatment with anticonvulsant drugs may affect the QTc interval in persons with epilepsy and could increase the risk of fatal ventricular arrhythmia.[11]

Efforts to determine the proximate causes of SUDEP have involved simultaneous recordings of brain, heart, and respiratory activity in human subjects being video monitored for seizure occurrence[12] and similar studies in rodent epilepsy models. In rats, treatment with kainic acid evokes a chronic seizure disorder, which has been associated with QTc prolongation and increased QT dispersion that may predispose to ventricular fibrillation under certain conditions.[13,14] However, the underlying mechanisms responsible for these electrophysiological phenomena were uncertain.

In the article by Biet et al[15] published in this issue of *Circulation: Arrhythmia and Electrophysiology*, the cellular and molecular basis for QT prolongation associated with kainic acid–induced epilepsy in rats was investigated. The investigators measured cardiac action potential duration and sodium currents in acutely isolated ventricular myocytes from epileptic rats and compared their findings with cells taken from nonepileptic rats. A prolonged action potential duration was observed in cardiomyocytes from the epileptic rats but not in cells from nonepileptic rats. Furthermore, the prolonged action potential duration could be rectified by exposure of cells to low nanomolar concentrations of tetrodotoxin, a specific blocker of voltage-gated sodium channels. The concentration of tetrodotoxin effective for normalizing action potentials in cardiomyocytes from the epileptic rats is insufficient to achieve a significant level of block of the dominant cardiac sodium channel isoform ($Na_V1.5$), which is relatively tetrodotoxin resistant. However, nanomolar tetrodotoxin is more than adequate to inhibit highly tetrodotoxin-sensitive neuronal isoforms (eg, $Na_V1.1$, $Na_V1.2$, $Na_V1.3$), some of which are expressed in cardiac tissue at low levels. Further supporting a possible contribution of neuronal sodium channels to action potential prolongation, the authors observed that a higher fraction of tetrodotoxin-sensitive sodium current was seen in cardiomyocytes from epileptic rats when compared with nonepileptic rats. This difference correlated with a significantly higher level of $Na_V1.1$ mRNA expression in epileptic rats and a corresponding change in protein levels. These findings suggest that chronic epilepsy alters cardiac expression of neuronal sodium channels.

How would augmented expression of $Na_V1.1$ in heart prolong the QTc interval? The investigators addressed this question by measuring the noninactivating fraction of sodium current (I_{Na}) known variably as late I_{Na} (I_{NaL}) or persistent I_{Na}. Cardiomyocytes from epileptic rats exhibited ≈50% greater total I_{NaL} than nonepileptic rats but there was a disproportionately larger fraction of I_{NaL} sensitive to low concentrations of tetrodotoxin. These data suggest that chronic epilepsy in the kainic acid–treated rats was associated with an increased level of I_{NaL} and that much of this increase was because of tetrodotoxin-sensitive sodium channels. The higher level of I_{NaL} offers a mechanism for prolonged action potential duration and for prolonged QTc interval analogous to type 3 congenital long-QT syndrome caused by gain-of-function mutations in the cardiac sodium channel ($Na_V1.5$). Furthermore, the mRNA and protein measurements suggest that higher expression

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of $Na_V1.1$ provides a plausible molecular explanation for increased tetrodotoxin-sensitive I_{NaL}.

The findings in this article offer new evidence for cardiac arrhythmia susceptibility as a substrate for SUDEP, at least in a rodent model of chronic epilepsy. The data also kindle interest in understanding the contribution of neuronal sodium channels to cardiac electrophysiology. As a next step, the transcriptional mechanisms responsible for greater cardiac expression of $Na_V1.1$ in chronic epilepsy rats should be explored. Factors such as altered autonomic tone, which is known to be associated with epilepsy, and the episodic metabolic (hypoxemia, academia, and hyperkalemia) and hormonal (catecholamine release) derangements that occur during seizures[16] could be provocateurs of these molecular events in the experimental animals.

Other rodent models of SUDEP have been used to investigate primary mechanisms responsible for death in epilepsy. Two intriguing mouse models of SUDEP involving genetic mutations of neuronal potassium ($K_V1.1$) or sodium ($Na_V1.1$) channels have been most intensively investigated. In the $K_V1.1$-null mouse model, postictal bradyarrhythmias have been shown to immediately precede death.[17,18] Aberrant parasympathetic neurotransmission is partly to blame for these cardiac events. Enhanced parasympathetic effects on heart causing interictal and postictal bradycardia were also identified as the immediate antecedents to SUDEP in heterozygous $Na_V1.1$ knockout mice, a model of the epileptic encephalopathy Dravet syndrome.[19] A more recent study using similar mouse models demonstrated the importance of brainstem spreading depression, a pathological wave of neuronal membrane depolarization that suppresses neuronal activity, as the neurophysiological mechanism trigging cardiorespiratory arrest following a seizure.[20] In these experimental animals, seizure-triggered brainstem spreading depression evoked apnea and bradycardia followed by asystole and death. Whether the mechanism underlying SUDEP in the kainic acid–induced chronic epilepsy rat model featured in the study by Biet et al[15] is similar or distinct awaits further investigation.

Do these findings in rodent models of SUDEP translate to humans with epilepsy? Several mostly small scale studies and anecdotal reports have attempted to correlate seizure events with cardiac and respiratory activity in persons with epilepsy. These efforts have exploited epilepsy monitoring units, where simultaneous video, electroencephalographic, electrocardiographic, and respiratory measurements can be correlated. Although few episodes of SUDEP have been captured, the majority of these studies have found a predominance of bradyarrhythmias rather than life-threatening tachyarrhythmias (eg, ventricular tachycardia or fibrillation) as the most common heart rhythms preceding SUDEP. For example, the Mortality in Epilepsy Monitoring Units Study (MORTEMUS) reported data collected from 16 cases of SUDEP and 9 cases of aborted SUDEP.[12] For 10 SUDEP cases in which there were complete cardiorespiratory monitoring data at the time of death, the final heart rhythm was bradycardia or transient asystole (>5 s duration) followed by terminal asystole. Transient episodes of apnea (>10 s) occurred concomitantly with abnormal heart rhythms followed by sustained apnea that preceded the final cardiac arrest. In just 1 case of near SUDEP involving a 51-year-old women, ventricular fibrillation occurred during a generalized tonic–clonic seizure and was implicated as the cause of cardiac arrest. Although not the predominant cause of SUDEP, ventricular tachyarrhythmia does appear to explain a small fraction of mortality in epilepsy.

The study by Biet et al[15] offers an intriguing mechanistic explanation for a subset of SUDEP associated with aberrant myocardial repolarization. How these findings obtained from an induced, chronic epilepsy rat model correspond to human SUDEP is uncertain, but there may be a subset of cases in which the identified mechanisms may be relevant. Although the findings of Biet et al,[15] do not identify the need for a specific therapeutic strategy, arrhythmia surveillance efforts in persons with epilepsy should carefully evaluate the QTc interval as a potential risk factor for SUDEP. Strategies to mitigate effects of medications or underlying heart disease on this risk should be considered when appropriate.

Disclosures

None.

References

1. Massey CA, Sowers LP, Dlouhy BJ, Richerson GB. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. *Nat Rev Neurol*. 2014;10:271–282. doi: 10.1038/nrneurol.2014.64.
2. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. *Lancet*. 2011;378:2028–2038. doi: 10.1016/S0140-6736(11)60176-1.
3. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures [published online ahead of print June 2, 2015]. *J Neurol Neurosurg Psychiatry*. doi: 10.1136/jnnp-2015-310559. http://jnnp.bmj.com/content/early/2015/06/02/jnnp-2015-310559.abstract.
4. Dasheiff RM, Dickinson LJ. Sudden unexpected death of epileptic patient due to cardiac arrhythmia after seizure. *Arch Neurol*. 1986;43:194–196.
5. Lamberts RJ, Blom MT, Wassenaar M, Bardai A, Leijten FS, de Haan GJ, Sander JW, Thijs RD, Tan HL. Sudden cardiac arrest in people with epilepsy in the community: circumstances and risk factors. *Neurology*. 2015;85:212–218. pii: 10.1212/WNL.0000000000001755.
6. Surges R, Taggart P, Sander JW, Walker MC. Too long or too short? New insights into abnormal cardiac repolarization in people with chronic epilepsy and its potential role in sudden unexpected death. *Epilepsia*. 2010;51:738–744. doi: 10.1111/j.1528-1167.2010.02571.x.
7. Brotherstone R, Blackhall B, McLellan A. Lengthening of corrected QT during epileptic seizures. *Epilepsia*. 2010;51:221–232. doi: 10.1111/j.1528-1167.2009.02281.x.
8. Surges R, Sander JW. Sudden unexpected death in epilepsy: mechanisms, prevalence, and prevention. *Curr Opin Neurol*. 2012;25:201–207. doi: 10.1097/WCO.0b013e3283506714.
9. Lamberts RJ, Blom MT, Novy J, Belluzzo M, Seldenrijk A, Penninx BW, Sander JW, Tan HL, Thijs RD. Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. *J Neurol Neurosurg Psychiatry*. 2015;86:309–313. doi: 10.1136/jnnp-2014-307772.
10. Nei M, Ho RT, Sperling MR. EKG abnormalities during partial seizures in refractory epilepsy. *Epilepsia*. 2000;41:542–548.
11. Feldman AE, Gidal BE. QTc prolongation by antiepileptic drugs and the risk of torsade de pointes in patients with epilepsy. *Epilepsy Behav*. 2013;26:421–426. doi: 10.1016/j.yebeh.2012.09.021.
12. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, Boon P, Crespel A, Dworetzky BA, Høgenhaven H, Lerche H, Maillard L, Malter MP, Marchal C, Murthy JM, Nitsche M, Pataraia E, Rabben T, Rheims S, Sadzot B, Schulze-Bonhage A, Seyal M, So EL, Spitz M, Szucs A, Tan M, Tao JX, Tomson T. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol*. 2013;12:966–977. doi: 10.1016/S1474-4422(13)70214-X.
13. Naggar I, Lazar J, Kamran H, Orman R, Stewart M. Relation of autonomic and cardiac abnormalities to ventricular fibrillation in a rat model of epilepsy. *Epilepsy Res*. 2014;108:44–56. doi: 10.1016/j.eplepsyres.2013.10.018.
14. Bealer SL, Little JG. Seizures following hippocampal kindling induce QT interval prolongation and increased susceptibility to arrhythmias in rats. *Epilepsy Res*. 2013;105:216–219. doi: 10.1016/j.eplepsyres.2013.01.002.

15. Biet M, Morin N, Lessard-Meaudoin M, Graham RK, Duss S, Gagné J, Sanon NT, Carmant L, Dumaine R. Prolongation of action potential duration and QT interval during epilepsy linked to increased contribution of neuronal sodium channels to cardiac late Na^+ current: potential mechanism for sudden death in epilepsy. *Circ Arrhythm Electrophysiol*. 2015;8:912–920. doi: 10.1161/CIRCEP.114.002693.
16. Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. *Nat Rev Neurol*. 2009;5:492–504. doi: 10.1038/nrneurol.2009.118.
17. Glasscock E, Yoo JW, Chen TT, Klassen TL, Noebels JL. Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy. *J Neurosci*. 2010;30:5167–5175. doi: 10.1523/JNEUROSCI.5591-09.2010.
18. Moore BM, Jerry Jou C, Tatalovic M, Kaufman ES, Kline DD, Kunze DL. The Kv1.1 null mouse, a model of sudden unexpected death in epilepsy (SUDEP). *Epilepsia*. 2014;55:1808–1816. doi: 10.1111/epi.12793.
19. Kalume F, Westenbroek RE, Cheah CS, Yu FH, Oakley JC, Scheuer T, Catterall WA. Sudden unexpected death in a mouse model of Dravet syndrome. *J Clin Invest*. 2013;123:1798–1808. doi: 10.1172/JCI66220.
20. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. *Sci Transl Med*. 2015;7:282ra46. doi: 10.1126/scitranslmed.aaa4050.

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