Current Literature

In Basic Science

Seizures, Epilepsy, and SUDEP: A Change of Heart?

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.

Biet M, Morin N, Lessard-Beaudoin M, Graham RK, Duss S, Gagné J, Sanon NT, Carmant L, Dumaine R. *Circ Arrhythm Electrophysiol* 2015;8:912–920.

BACKGROUND: Arrhythmias associated with QT prolongation on the ECG often lead to sudden unexpected death in epilepsy. The mechanism causing a prolongation of the QT interval during epilepsy remains unknown. Based on observations showing an upregulation of neuronal sodium channels in the brain during epilepsy, we tested the hypothesis that a similar phenomenon occurs in the heart and contributes to QT prolongation by altering cardiac sodium current properties (I_{Na}). **METHODS AND RESULTS:** We used the patch clamp technique to assess the effects of epilepsy on the cardiac action potential and I_{Na} in rat ventricular myocytes. Consistent with QT prolongation, epileptic rats had longer ventricular action potential durations attributable to a sustained component of I_{Na} (I_{NaL}). The increase in I_{NaL} was because of a larger contribution of neuronal Na channels characterized by their high sensitivity to tetrodotoxin. As in the brain, epilepsy was associated with an enhanced expression of the neuronal isoform Na_v1.1 in cardiomyocyte. Epilepsy was also associated with a lower I_{Na} activation threshold resulting in increased cell excitability. **CONCLUSIONS:** This is the first study correlating increased expression of neuronal sodium channels within the heart to epilepsy-related cardiac arrhythmias. This represents a new paradigm in our understanding of cardiac complications related to epilepsy.

Commentary

Sudden unexpected death in epilepsy (SUDEP) is defined by the sudden, unexplainable death of an individual with epilepsy and accounts for approximately 17% of epilepsy-related deaths. Patients with longstanding epilepsy characterized by frequent generalized tonic-clonic seizures that are relatively poorly controlled appear to be at highest risk. Physiological factors that may contribute to SUDEP include peri-ictal, centrally-originating autonomic irregularities leading to cardiac and respiratory arrest. Electrocardiographic abnormalities characterized mainly by rhythm and repolarization changes, including prolonged QT interval, are also associated with the occurrence of generalized seizures in patients with epilepsy and may contribute to SUDEP, especially when it occurs postictally (1). Similar to clinical reports, arrhythmias associated with altered cardiac Na⁺ channel function have been demonstrated in rodent epilepsy models, including the kainate-induced status epilepticus model of temporal lobe epilepsy (TLE) (2), but the mechanisms supporting these changes were previously undescribed. Biet and colleagues investigated epilepsy-related changes in several Na⁺ currents that underlie action potential repolarization and timing in cardiomyocytes as they relate to cardiac conduction and excitability. Significant functional and molecular cardiac channel remodeling was detected in

conjunction with development of spontaneous seizures in the TLE model, consistent with epilepsy-induced overexpression of a neuronal Na⁺ channel isoform in cardiomyocytes, which predispose to an increase in QT interval.

Normally, cardiomyocyte action potential generation and inactivation are tightly regulated in order to maintain appropriate cardiac contraction rhythms. As in central neurons, cardiac action potentials are mediated by Na⁺ currents, although neuronal and cardiomyocyte Na⁺ currents differ in their kinetics and are composed of different channel isoforms. Cardiac Na⁺ currents are mediated mainly by a relatively tetrodotoxin (TTX)-insensitive Na⁺ channel isoform, Na_v1.5, encoded by the *SCN5A* gene, which imparts relatively fast activation and inactivation kinetics. Normally, Na⁺ currents and action potentials in neurons are mediated by a TTX-sensitive Na⁺ channel isoform, Na_v1.1, which has somewhat slower kinetics and is encoded by the *SCN1A* gene. Using electrophysiological recordings in vitro, the authors found that action potential duration was increased in cardiomyocytes from epileptic rats, and TTX was more potent in reducing action potential duration and peak Na⁺ current amplitude in epileptic rats than in controls. Activation threshold was also hyperpolarized relative to controls. Interestingly, these changes were very similar to Na⁺ current increases reported in hippocampal neurons from spontaneously epileptic rats (3). Increased activation of a late Na⁺ (Na_L) current tends to increase cardiac action potential duration, which can result physiologically in increased QT interval that can lead to long QT syndrome and other arrhythmias. The TTX-sensitivity of the Na_L current was also enhanced in cardiomyocytes from epileptic rats.

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Together, these findings suggested an increased contribution of the TTX-sensitive, brain-associated $\text{Na}_v1.1$ channel isoform to cardiomyocyte Na^+ channel activity and cardiac rhythm regulation. Consistent with the electrophysiological findings, relative mRNA expression of the brain *SCN1A* gene was significantly increased in cardiomyocytes. Increased expression of neuronal Na^+ channels in cardiomyocytes may, therefore, underlie altered conduction properties that support cardiac arrhythmia associated with epilepsy development in this model.

Long QT syndrome has been reported previously to develop after status epilepticus in rats, and this arrhythmia may contribute to sudden death after seizure. Although sudden death in people with long QT syndrome is rare, there is little doubt that the arrhythmia can contribute to cardiac failure. The de novo development of prolonged QT interval during epileptogenesis could, therefore, underlie some cases of SUDEP. The novel findings of Biet and colleagues indicate that functional cardiac channel remodeling occurs in conjunction with epilepsy development in this model, and this remodeling is due to relative overexpression of the brain-dominant *SCNA1* gene in the heart after seizures. Mechanistic triggers of cardiac remodeling leading to channel dysfunction and arrhythmia are not known, and nor is the relationship between seizures and changes in cardiac channel expression understood. Ictal tachycardia and dysrhythmia, including prolonged QT interval, and postictal bradycardia and asystole accompanied by dysregulated respiration and hypoxia can accompany individual seizures (4); thus, ongoing, epilepsy-associated Na^+ channel remodeling could compound the acute changes in cardiac function that are associated with individual seizures. There is currently no consensus about the cause(s) of SUDEP, but derangement of cardiac and/or respiratory function is the primary focus of much research on this topic. A gradual, seizure-induced remodeling of cardiac function, superimposed on episodic seizure events, could help explain why the first seizure is not the last seizure in most SUDEP cases.

In addition to cardiac arrhythmia and altered heart rate variability, apnea and eventual respiratory failure are currently hypothesized to be causes of SUDEP. Interestingly, postictal generalized suppression of the EEG was reported in the few SUDEP patients that have been monitored electrographically, which leads to autonomic dysregulation (5, 6). Seizures can spread centrally to activate midbrain arousal areas or medullary neurons that control vagus nerve functions (4, 7) and activity-dependent plasticity in central vagal neurons occurs in a variety of diseases (8, 9). Because seizures can alter responsiveness of brainstem neurons that integrate cardiorespiratory functions, it seems reasonable to speculate that seizure-related neuroplasticity in the brainstem might eventually develop in epilepsy to influence both cardiac and respiratory functions (7). Changes in how the brainstem regulates cardiorespiratory functions may be compounded by intrinsic cardiac arrhythmias that develop due to cardiomyocyte expression of neuronal Na^+ channels.

A potentially important feature of the study by Biet et al. is that rather than using a genetic model of pediatric epilepsy like the *SCNA1* mutant Dravet mouse, the authors detected cardiac channel reorganization in a rat model of adult,

acquired TLE that developed spontaneous recurrent seizures. Thus, changes in cardiomyocyte Na^+ channel function were most likely related to epilepsy development and not genetic influences. There has been a basic science research emphasis on studying SUDEP in genetic models of epilepsy, probably because of the relatively high risk of SUDEP in young patients with genetic epilepsies. However, SUDEP can occur in many epilepsies, including TLE, and adults 21 to 50 years of age with long histories of uncontrolled seizures are most commonly susceptible to SUDEP (10). In fact, patients with TLE represent approximately 60% of all epilepsies, supporting the relevance of identifying cardiac and other changes associated with spontaneous seizures in this model. A mechanistic understanding of how epileptogenesis increases susceptibility to catastrophic physiological systems failure will be critical in developing therapies to prevent SUDEP. The study by Biet and colleagues highlights the importance of considering epilepsy-related peripheral plasticity in addition to effects on the brain.

by Bret N. Smith, PhD

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