Scurrying to Understand Sudden Expected Death in Epilepsy: Insights From Animal Models

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Abstract
Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with refractory epilepsy, accounting for up to 17% of deaths in patients with epilepsy. The pathophysiology of SUDEP has remained unclear, largely because it is unpredictable and commonly unwitnessed. This poses a great challenge to studies in patients. Recently, there has been an increase in animal studies to try to better understand the pathophysiology of SUDEP. In this current review, we focus on developments through seizure-induced death models and the preventative strategies they may reveal.

Keywords
SUDEP, death, breathing, cardiac, arousal, animal models

Introduction
Epilepsy affects more than 70 million people globally.\(^1\) Although seizures can be fatal in several ways,\(^2\) sudden unexpected death in epilepsy (SUDEP) accounts for up to 17% of death in patients with epilepsy.\(^3\) Sudden unexpected death in epilepsy is second only to stroke in potential life-years lost due to neurological disease.\(^4\) Sudden unexpected death in epilepsy is defined as the sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in a patient with epilepsy, excluding known status epilepticus and in who the postmortem examination provides no structural or toxicological causes of death.\(^5\) Sudden unexpected death in epilepsy most commonly follows a seizure, especially a generalized one.\(^6\) Other risk factors include young age of onset, poor medication compliance, nocturnal seizures, sleeping prone, long seizure duration, and long epilepsy history.\(^7,8\) The landmark MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) demonstrates a cascade of cardiorespiratory events preceding death,\(^9\) suggesting SUDEP is the consequence of a complex and heterogeneous process. Proposed pathophysiological mechanisms for SUDEP include respiratory, cardiac, and arousal dysregulation and have implicated several neurotransmitter and neuromodulator systems.\(^2,7,10-12\) The unpredictable and largely unwitnessed nature of SUDEP poses a great challenge to studies in patients. Herein, we will review basic science developments in SUDEP research, focusing primarily on animal models (Table 1) in the context of etiology they recapitulate and preventative strategies these models may reveal.

Respiratory Mechanisms
Seizures frequently affect breathing.\(^6,5\) In patients who succumbed to SUDEP in epilepsy monitoring units in the MORTEMUS study, terminal apnea preceded terminal asystole.\(^9\) To better understand mechanisms for how seizures affect breathing, several groups have turned to animal models.

Several animal models recapitulate a seizure-induced respiratory arrest (S-IRA) phenotype. Perhaps the most well-known models are the DBA/1 and DBA/2 mouse audiogenic seizure (AGS) models. These mice commonly exhibit S-IRA following AGS. S-IRA can be rescued by mechanical ventilation.\(^3\) If resuscitation is delayed, mice will then develop cardiac arrhythmia and eventually die from the AGS.\(^3\) While DBA/1...
Table 1. A Summary of Animal Models in the Context of SUDEP Etiology.

| Animal Model                                      | Major Findings in Mechanism and Prevention/Intervention                                                                 |
|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| **DBA mouse audiogenic seizure**                  | Seizure-induced respiratory arrest is followed by cardiac arrhythmia and death.                                               |
|                                                   | Serotonin (S-HT) receptor distribution is different.                                                                     |
|                                                   | Increasing S-HT or norepinephrine improves S-IRA and mortality, and vice versa.                                          |
|                                                   | Reduced periaqueductal gray-mediated cardiorespiratory compensatory mechanism.                                             |
|                                                   | Caffeine can prevent S-IRA through adenosine A2A receptors.                                                              |
| **Lmx1b<sup>fl/fl</sup> mouse maximal electroshock**| Seizure severity and dysregulation of breathing after MES seizures in mice is increased during sleep and during light phase |
| (MES)-induced seizure model                       | Increasing S-HT or NE or both improves S-IRA and death.                                                                  |
| **SCN1A mutant Dravet syndrome mouse models**     | Death can be prevented by mechanical ventilation and atropine.                                                           |
|                                                   | Hypoventilation, apnea, and blunted responses to CO₂ owing to changes in neuronal excitability in retrotrapezoid nucleus. |
|                                                   | The severity of SCN1A deficiency is brain region dependent.                                                               |
|                                                   | Cardiac arrhythmia and reduced interictal resting heart rate variability is observed along with spontaneous death, and the ictal bradycardia leading to SUDEP can be improved by atropine or N-methyl scopolamine. |
|                                                   | A delayed maturation of GABAergic signaling may contribute to epileptogenesis in this model.                              |
|                                                   | Mice have a lower threshold for spreading depolarization, and neurons derived from patients with Dravet syndrome show hyperexcitability, and cardiac myocytes show increased spontaneous contraction rates. |
|                                                   | Abnormal sleep architecture but not total sleep duration probably due to an imbalance between excitatory and inhibitory neurons in the thalamocortical network. |
| **KCNA1 null mouse model**                        | Progressively worsened respiratory dysfunction with abnormal breathing pattern always precedes cardiac abnormalities during ictal phase. |
|                                                   | Cardiac abnormalities that are more frequent during seizure.                                                            |
|                                                   | The tau encoding gene deletion that results in an increased life expectancy also restored the normal spreading depolarization threshold in the brainstem. |
|                                                   | SCN2A deletion improves survival rate in the KCNA1-null mice.                                                           |
|                                                   | Prolonged circadian periods and increased wake time along with attenuated oscillation of several clock genes.           |
|                                                   | Ketogenic diet reduces seizure number, extends life expectancy, and corrects the rest deficiency of which the chronic accumulation contributes to the majority of death. |
|                                                   | With genetic knockout of BCL2-associated agonist of cell death protein, KCNA1-null mice survive longer and have a less sever phenotype. |
| **Status epilepticus sheep model**                | Commonalities in mechanisms of death between status epilepticus and SUDEP.                                                |
| **Epileptic baboon model**                        | Sudden unexpected death with similar pathology to SUDEP.                                                                 |
| **Kainic acid–induced acute seizure model**       | Glottic closure precedes cardiac arrhythmia and death; preventing obstructive terminal apnea caused by a large pH reduction within the esophagus can prevent death. |
| **Pilocarpine-induced chronic seizure model**     | Reduced survival rate with a higher basal heart rate probably due to altered autonomic modulation.                      |
|                                                   | GABAergic neurons in the nucleus tractus solitarius have an increased excitability.                                       |
|                                                   | Lower survival rate with no obvious causes of death.                                                                     |
|                                                   | A decreased neuronal density in the nucleus tractus solitarius and decreased vagal tone and increased QT dispersion.      |
|                                                   | Increased splanchnic sympathetic nerve activity with increased heart rate, which can be blocked by microinjecting glutamate antagonist into the rostral ventrolateral medulla. |
| **Wistar audiogenic seizure rat model**           | An increased basal systolic arterial pressure and heart rate, and the major causes of death are dysautonomia and cardiac dysfunction. |
| **A murine model of postinfection acquired epilepsy** | The abnormal cortical discharge caused cardiac arrhythmia can be detected weeks before the first seizure onset.              |
| **SCN8A mutant mouse model**                      | Spontaneous seizure and premature death in a dose- and brain region–dependent manner.                                    |
| **RYR2 mutant mouse model**                       | Spontaneous seizure and sudden death are rare, but when provoked, cortical seizures frequently led to apneas, brain stem spreading depolarization, cardiorespiratory failure, and death. |
| **Tetanus toxin-induced chronic seizure model**    | Much higher seizure frequency in rapid eye movement sleep.                                                              |

Abbreviations: NE, norepinephrine; S-IRA, seizure-induced respiratory arrest; SUDEP, sudden unexpected death in epilepsy.
mice usually need several stimuli before consistently showing AGS with S-IRA, DBA/2 mice are more likely to have an S-IRA in their first AGS. This phenomenon can at least be partially attributed to the difference in serotonin 5-hydroxytryptamine (5-HT) receptor expression. Selective 5-HT reuptake inhibitors such as fluoxetine and sertraline, and a 5-HT-releasing drug fenfluramine, reduce the likelihood of S-IRA, whereas a nonselective 5-HT receptor antagonist cyproheptadine facilitates occurrence of S-IRA in DBA mice. Optogenetic activation of 5-HT neurons suppresses S-IRA in the DBA/1 mice. An insufficiency in the periaqueductal gray-mediated cardiorespiratory compensatory mechanism which can be enhanced by fluoxetine may underlie the death of DBA/1 mice. 5-HT2C receptor-null mutant mice are also susceptible to AGS and death. Mice with a genetic deletion of 5-HT neurons in the central nervous system (Lm1xβ/β) show increased susceptibility to and mortality from chemically and electrically induced seizures. These mice demonstrate S-IRA following maximal electroshock (MES)-induced seizures, which can be prevented by 5-HT3A receptor agonists. This evidence suggests 5-HT plays an important role in S-IRA and SUDEP. Norepinephrine (NE) also regulates arousal and respiration in the brain. An NE reuptake inhibitor (NRI) atomoxetine suppresses the S-IRA in the DBA/1 mice. Ato- moxetine and another NRI, reboxetine, also reduce S-IRA following MES-induced seizures. This suggests a role for NE in modulating S-IRA and death.

The role of airway obstruction in SUDEP has also been explored. Recurrent seizures induced with kainic acid, a glutamate receptor agonist, in anesthetized Sprague Dawley rats, result in complete glottic closure which is followed by ST-segment elevation, bradycardia, and eventually death, while central apnea only causes minimal cardiac changes. In another study, laryngospasm which causes obstructive terminal apnea is accompanied by a large pH reduction within the esophagus. More importantly, when obstructive apnea is prevented by blocking the acidification, there are no sudden deaths, suggesting a novel strategy for intervention.

Peri-ictal and postictal respiratory dysfunction have also been identified in genetic mouse models. Dravet syndrome, a childhood-onset epileptic encephalopathy which often progresses into a refractory epilepsy, is associated with a high SUDEP risk. Mutation in SCN1A encoding the Nav1.1 voltage-gated sodium channel is found in 80% of patients with Dravet syndrome. In SCN1AR1407X/+ mice, death can be prevented by mechanical ventilation and intracerebroventricular infusion of atropine, suggesting a central apnea mechanism in these cases with SUDEP. Likewise, mice carrying a conditional SCN1A missense mutation exhibit hypoventilation, apnea, and blunted response to CO2 which can be explained by changes in neuronal excitability in the retrotrapezoid nucleus. Mice lacking the Kv1.1 channel encoded by the KCNA1 gene have early-onset seizures and subsequent SUDEP. An array of respiratory dysfunction that progresses with age has been found in KCNA1-null mice, and the abnormal breathing pattern always precedes cardiac abnormalities during the ictal phase.

In addition, a sheep model of bicuculline-induced status epilepticus reveals a doubled peak pulmonary vascular pressure without cardiac changes and a rapid rise in serum (CO2) and rapid drop in serum (O2) in animals that died. Baboons with genetic generalized epilepsy are more likely to die young without apparent cause except pulmonary edema, which suggests death from SUDEP.

Cardiac Mechanisms

Seizures commonly affect cardiac function. Cardiac dysrhythmias have been implicated in SUDEP. A number of animal models demonstrate seizure-associated cardiac phenotypes that may be useful in understanding the pathophysiology of SUDEP.

Rats with epilepsy induced by the administration of pilocarpine, a cholinergic muscarinic agonist, have a higher basal heart rate compared to controls. Mice subjected to pilocarpine have a lower survival rate compared to age-matched controls. GABAergic neurons in the nucleus tractus solitarius (NTS), a key locus in cardiorespiratory regulation, of these mice display a glutamate-dependent increase in spontaneous action potentials and reduced A-type potassium current, suggesting increased excitability likely contributing to reduced survival. Similarly, rats subjected to kainic acid-induced epilepsy have a high mortality rate at 24 months, which has been attributed to SUDEP. These rats have decreased neuronal density in the NTS, decreased vagal tone, and increased QT dispersion. In addition, they show a 2-fold increase in splanchnic sympathetic nerve activity with increased heart rate, which can be blocked by microinjecting a glutamate antagonist into the rostral ventrolateral medulla.

When subjected to acoustic stimulation, Wistar audiogenic rats can have AGSs and die from them. These rats show an increased basal systolic arterial pressure and heart rate, and the major causes of death are dysautonomia and cardiac dysfunction. In a murine model of postinfection-acquired epilepsy which has an SUDEP phenotype, cardiac arrhythmia is preceded by abnormal cortical discharges, and this brain–heart interaction can be detected weeks before the first seizure onset, supporting the idea that cardiac abnormalities originate in the brain.

Some genes that cause cardiac arrhythmia, such as long QT syndrome, are also involved in SUDEP. For example, both the SCN1A-deficient models and the knock-in mouse model of the human mutation SCN1AR1407X+ recapitulate characteristic seen in patients. Reduced interictal resting heart-rate variability has been found in the SCN1A-deficient model, and the ictal bradycardia leading to SUDEP can be improved by atropine or N-methyl scopolamine. SCN1AR1407X+ mice display a range of cardiac abnormalities including QT prolongation, ventricular fibrillation, and focal bradycardia. Interestingly, the effect of SCN1A deficiency is brain region dependent. The lack of Nav1.1 in inhibitory GABAergic neurons causes a more
A possible mechanism that contributes to SUDEP in these animal models is spreading depolarization, a self-propagating depolarizing wave that silences neuronal networks. A lower threshold for spreading depolarization has been found in SCN1A mutant mice, KCNA1-null mice, Cacna1a<sup>218L</sup>, and RYR2<sup>Q0+/-</sup> mice. Although spontaneous seizure and sudden death are rare in RYR2<sup>Q0+/-</sup> mice, when provoked, cortical seizures frequently lead to apneas, brainstem spreading depolarization, cardiorespiratory failure, and death due to enhanced excitation in cortex and brainstem autonomic microcircuits. These findings indicate a causal relationship between spreading depolarization and SUDEP.

An interesting way to explore effects of mutation on cellular function is to use induced pluripotent stem cells (iPSCs) from patients with epilepsy. Forebrain-like pyramidal- and bipolar-shaped neurons derived from patients with Dravet syndrome show increased sodium currents, spontaneous firing, and other signs of hyperexcitability compared to neurons derived from healthy controls. Cardiac myocytes derived from iPSC of patient with Dravet syndrome show increased sodium current and spontaneous contraction rates. Remarkably, cardiac abnormalities identified from iPSC-derived cardiac myocytes were confirmed clinically for the subject with the most profound increase in sodium current, suggesting patient-derived iPSCs are a valuable tool for risk assessment. Progress has also been made in other neurological diseases that have a seizure phenotype such as Rett syndrome using the iPSC platform.

**Arousal, Sleep, and Time of Day**

In 7 of the 10 cases from the MORTEMUS study for which adequate data were available to determine vigilance state, SUDEP occurred following nocturnal seizures. Seizure severity and dysregulation of breathing after MES seizures in mice is increased during sleep and during the inactive phase. An SCN1A haploinsufficiency Dravet syndrome mouse model shows abnormal sleep architecture but not total sleep duration probably due to an imbalance between excitatory and inhibitory neurons in the thalamocortical network.

**Conclusions**

Sudden unexpected death in epilepsy is an important public health problem. Before preventive strategies can be implemented, we need to better understand the pathophysiology. Basic science studies, especially those involving animal models, are rapidly advancing our understanding of the pathophysiology of SUDEP. An important way forward will be to continue to develop models that recapitulate as many key features of human SUDEP as possible.

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