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Mechanisms of sudden unexplained death in epilepsy

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Abstract

Purpose of review—Human and experimental research has identified cardioautonomic and respiratory dysfunction as a frequent accompaniment in human and animal model events of sudden unexpected death in epilepsy (SUDEP). This review aims to provide an overview of the scientific evidence behind the currently accepted risk factors and working hypotheses regarding SUDEP pathophysiology.

Recent findings—Epidemiological analysis of public health burden of SUDEP has shown that it rates second only to stroke in the years of potential life lost. Clinical and experimental studies uncovered the dynamic cardiorespiratory dysfunction interictally and imminently to SUDEP, and model systems have facilitated discoveries in SUDEP mechanistic understanding and application of pilot therapeutic interventions. Pilot molecular profiling of human SUDEP has uncovered complex genomic structure in the candidate gene network.

Summary—Extensive clinical and experimental work has established a rationale for the conceptual thinking about SUDEP mechanisms. The application of the global molecular profiling will be invaluable in unraveling the individually unique genomic complexities and interactions that underlie the physiological signature of each patient. At the same time, sophisticated model systems will be critical in the iterative translation of human genetics, physiology, pharmacological interventions, and in testing preventive interventions.

Keywords

epilepsy; gene; mechanisms; sudden unexpected death in epilepsy

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is a sudden unexpected witnessed or unwitnessed mortality in otherwise healthy patients with epilepsy with or without evidence of a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a cause of death [1]. If a patient is successfully resuscitated following a cardiopulmonary arrest, the event is classified as near-SUDEP [1]. SUDEP is the most frequent epilepsy-related cause of death, second only to stroke in the years of productive life lost [2■■]. Although SUDEP is most common among young adults with frequent, medically

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Conflicts of interest

There are no conflicts of interest.

refractory seizures [3], it can affect children [4] and patients with seemingly well controlled epilepsy [5]. Therefore, our efforts for prevention critically depend upon understanding SUDEP physiology and the individually relevant profile of clinical and molecular risk factors. This review aims to provide an overview of the clinical and experimental evidence behind the currently accepted risk factors and working hypotheses regarding SUDEP pathophysiology.

SUDDEN UNEXPECTED DEATH IN EPILEPSY RISK FACTORS AND CANDIDATE MECHANISMS

Role of epilepsy and seizures

Lack of seizure remission has been the major risk factor identified in many epidemiological studies [3]. As few as one to two annual generalized tonic-clonic seizures triple the SUDEP risk, whereas mortality hazard in patients with yearly frequency of 50 or more generalized tonic-clonic seizures is increased more than 14 times [3]. Direct observation of rare SUDEP and near-SUDEP instances in patients in the epilepsy monitoring units showed that death would usually occur following a partial or generalized seizure and at night [6,7■].

Role of the postictal generalized electroencephalographic suppression in sudden unexpected death in epilepsy

Postictal generalized electroencephalographic suppression (PGES) is a relatively frequent accompaniment of generalized tonic seizures [8]. In adults, it is often accompanied by elevated end-tidal CO₂ and often profound and prolonged hypoxemia [9]. In children, it tends to be shorter [8] and associated with both peri-ictal tachycardia and hypoxemia [10■]. Freitas *et al.* [8] found that the PGES duration negatively correlated with the extent of depression in the vagally mediated heart rate variability (HRV), although this connection was not replicated by others [11]. PGES-related SUDEP risk attribution is currently unclear [12,13].

Role of peri-ictal cardiopulmonary complications in sudden unexpected death in epilepsy

Studies in healthy individuals showed that both hypoxemia and hypercapnia can affect cardiac repolarization and shift autonomic balance toward the enhanced sympathetic drive on the sinus node [14,15]. Seyal *et al.* [16] found a positive correlation between the extent of ictal oxygen desaturation and the degree of cardiac repolarization abnormalities in epilepsy patients and the SUDEP case review in the Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) study [7■] revealed complex and ultimately lethal cardiopulmonary dysfunction early following a seizure (Fig. 1). Review of cardiopulmonary functions in 101 seizures in 26 children uncovered that approximately 50% of seizures were associated with apnea, and oxygen desaturation was associated with ictal bradycardia [17].

Molecular mechanisms and genetics of respiratory dysfunction in sudden unexpected death in epilepsy

Studies of telemetry-monitored patients equipped with complete plethysmography have been invaluable in gaining insight into the mechanisms of the seizure-related respiratory distress

[18,19]. Nashef *et al.* [18] found oxygen desaturations below 85% in 21% of all seizures and central apnea in 59% of patients and 42% of seizures. Bateman *et al.* [20] showed that ictal hypoxemia could last over 300 s, and the depth of desaturation correlated with seizure duration and spread to contralateral hemisphere. Moreover, oxygen desaturations below 85% were associated with the rise in the end-tidal CO₂ that in some patients persisted despite an increase in respiratory rate [20], thus indicating a primary pulmonary dysfunction rather than hypoventilation [19]. Animal models have provided valuable insight into the molecular underpinnings of seizure-induced respiratory dysfunction with lethal outcome. Tendency for ictally induced respiratory arrest and death following a tonic extension phase of seizure was first noted in the *Htr2c*-deficient mice [21]. The important role of serotonin [5-hydroxytryptamine (5-HT)] in respiration, arousal, and epileptic seizures was subsequently elucidated through the genetically engineered *Lmx1bf/f/p* mice deficient in more than 99% of 5-HT neurons and affected by severe apnea, hypoventilation, diminished hypercapnic response, and compromised arousal from sleep [22]. The animals also exhibited lower threshold for maximal electroshock or pilocarpine-induced seizures and increased seizure-related mortality driven by terminal respiratory failure [23]. Chemical inhibition of 5-HT synthesis in otherwise healthy mice reproduced the propensity for maximal electroshock induced seizures [23]. Altered expression of the 5-HT_{2c}, 5-HT₃, 5-HT₄, and 5-HT_{2B} receptors was shown in the DBA/2 mouse prone to respiratory arrest and death triggered by audiogenic seizures [24]. The discoveries linking respiratory failure and SUDEP led to preliminary pharmacological explorations of the widely available serotonin reuptake inhibitors (SSRIs) with respect to the SUDEP risk [25,26]. The exogenous administration of fluoxetine ameliorated seizure severity and ictally induced respiratory arrest and death in the DBA model in a dose-dependent fashion [26], whereas it improved the inherent serotonin deficiency and low ventilatory sensitivity to hypercapnia in the Brown Norway rats [27]. The animal research was subsequently validated in a cohort of patients with epilepsy chronically exposed to the commonly used SSRIs [28] that exhibited a reduced severity of ictal desaturation less than 85% during a partial seizure, albeit the effect was not seen during the secondarily generalized seizures [28]. Re-evaluation of the DBA model showed that the SSRI effect may vary according to drug, dosing, medications kinetics, age, and sex [29,30]. Although there is the translational evidence implicating the 5-hydroxytryptamine (5-HT) 2c receptor receptor in SUDEP, the role of the remaining 5-HT ligand-gated ion channels is largely unexplored. Large meta-analysis of patients affected by obstructive sleep apnea found that -1438G/A polymorphism in the *HTR2A* gene was a positive risk factor for obstructive sleep apnea in male patients [31], and a recent genetic analysis of a pediatric SUDEP case [32] suggested a contributory role of the inherited variants in the serotonergic receptor genes *HTR3C* and *HTR3D* that display altered expression in the DBA model [24]. Aside from the 5-HT pathways, the paired-like homeobox 2b (*PHOX2B*) gene has emerged as a candidate SUDEP molecule because of the previously described link to the central hypoventilation syndrome [33] and sudden infant death syndrome [34]. However, the initial screen of 68 Australian SUDEP cases indicates that detrimental mutations in this gene may not be a common SUDEP risk factor [35].

Molecular mechanisms and genetics of cardioautonomic dysfunction in sudden unexpected death in epilepsy

Cardioautonomic changes are observed in up to 42% of patients with refractory partial epilepsy monitored with a loop recorder [36]. Potentially serious dysrhythmias are seen in about 10% of patients and 6% of seizures [37]. Impaired cardiac recovery and repolarization abnormalities reflected in the depressed heart rate variability (HRV) and elevated values of the T-wave alternans were seen following the secondarily generalized seizures [38]. Meta-analysis of the HRV measure of epilepsy patients in 39 studies revealed consistent impairment of vagally driven activity with more profound HRV depression in individuals with refractory epilepsy [39]. Moreover, patients with refractory temporal lobe epilepsy (TLE) followed for an average of 6 years showed progressive depression of HRV measures over time in contrast to the well controlled TLE group [40]. Although the differences between patient groups did not reach statistical significance [40], this study was in line with the report of a SUDEP case with documented progressive deterioration of HRV variability and vagally mediated autonomic measure over several months preceding death [41]. Progressive autonomic changes were also noted in a recently published SUDEP case that displayed gradual rise in the parasympathetic activity over 7 months leading up to the terminal seizure. Additionally, ECG analysis revealed abnormally short QTc interval and clinically silent interictal episodes of supraventricular tachycardia [42].

Cardiac arrhythmia genes and sudden unexpected death in epilepsy

The first link between genetically predisposed cardiac arrhythmias and epilepsy was the discovery that the cardiac voltage-gated sodium channel *SCN5A*, underlying the long QT syndrome (LQTS) type 3 was expressed in the brain limbic regions [43]. Subsequent clinical case reports supported the concept of a combined neurocardiac phenotype triggered by a mutation in an ion channel dually expressed in the brain and in the heart [44,45]. The *SCN5A* nonsynonymous variant R523C with a predicted detrimental effect was found in a young woman affected by idiopathic epilepsy and peri-ictal cardiac palpitations [44] treated with lamotrigine and amitriptyline, medications with known effect on ion channels [46–49]. Her sudden death in the context of the *SCN5A* variant raised the possibility of an occult, pharmacologically triggered LQTS [44]. Another functionally detrimental de-novo *SCN5A* variant (R1623Q) was identified in a case of dual phenotype of neonatal seizures and long QT syndrome [45]. The initial mechanistic understanding of the complex phenotype of epilepsy, cardiac arrhythmias, and SUDEP came from transgenic mice carrying the human knock-in mutations in the most common *LQT* gene, the potassium channel *KCNQ1* [50]. The gene showed regional expression in the murine hippocampus, thalamus, and the medullary dorsal motor nucleus of the vagus and nucleus ambiguus, the brainstem centers contributing preganglionic parasympathetic innervation via the vagal nerve to the heart. The animals displayed partial and generalized seizures together with a variety of cardiac arrhythmias, and more than two-thirds of the cardiac abnormalities occurred in association with epileptiform discharges [50]. The lockstep phenomenon of recurrent brief asystole triggered by interictal epileptiform discharges has also been observed in other genetic models [51] and clinically [52]. The link between the epilepsy phenotype and LQTS has been clinically validated [53,54]. A seizure phenotype was identified in 28% of cases with clinically evident and genetically confirmed LQTS caused by pathogenic variants in the

KCNH2, *KCNQ1*, and *SCN5A* genes [54]. Molecular survey of these three genes in 68 SUDEP cases uncovered nonsynonymous variants of suspected functional significance in 10% of patients [55]. However, the molecular underpinnings of neurocardiac interactions encompass genes outside of the LQT syndrome channels [56]. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a dysrhythmia of young individuals presenting with stress-induced syncopal events due to ventricular tachycardia at high risk for sudden death before the age of 30 [57]. The underlying defect is in the ryanodine receptor gene (*RYR2*) [58] expressed in cardiac myocytes and also in the Ammon's horn and dentate gyrus of the mouse hippocampus [59]. A mutation leads to intracellular Ca^{2+} overload triggering early and delayed cardiac afterdepolarizations implicated as the pathological basis for the malignant bidirectional ventricular tachycardia [58]. The mouse model carrying the human mutation R2474S mirrored the human phenotype of exercise-induced ventricular arrhythmia, spontaneous convulsive seizures, and lethal arrhythmia triggered sudden death [60]. The combined phenotype of arrhythmias and seizures was observed in 12 of the 24 prospectively followed Dutch CPVT families affected by *RYR2* mutations [57]. Moreover, molecular autopsy of an 8-year-old SUDEP patient with history of epilepsy and recurrent, exercise-induced syncope with normal resting electrocardiogram (ECG) revealed a missense mutation G4936A of the *RYR2* channel in a screen of the principal LQT susceptibility genes [61]. The hyperpolarization-activated cyclic nucleotide-gated ion channels *HCN1–4* are members of another dually expressed gene family. They are implicated in epilepsy and cardiac arrhythmias owing to their involvement in the generation of the cation (Na and K)-triggered I_h depolarizing current that facilitates action potential critical for spontaneous rhythmic activity in the neurons and pacemaking cardiomyocytes [62–66]. A mouse deficient in *HCN2* displays the dual phenotype of absence epilepsy and sinus arrhythmia [67] albeit without an evidence of a reduced life span. Clinically confirmed dual epilepsy–arrhythmia phenotype has not yet been observed, although HCN channel mutational screen in 48 SUDEP cases uncovered nine coding variants, and in-silico prediction indicated functional significance for some [68]. As the biology of HCN channels in SUDEP remains to be defined, their involvement in clinically manifested arrhythmia or epilepsy warrants consideration of this gene family in the candidate *SUDEP* gene pool.

Epilepsy genes and sudden unexpected death in epilepsy

The potential number of novel candidate genes for SUDEP extends beyond those currently recognized in cardiac arrhythmias. The voltage-gated potassium channel *KCNA1* is dually expressed in brain and in the vagus nerve, and *Kcna1*-null mice have seizures, cardiac arrhythmias, and vagal hyperexcitability, and they die prematurely [51]. In this model, seizures clearly exacerbated the cardiac abnormalities as evidenced by the five-fold increase in the atrioventricular conduction block rate. Pretreatment with atropine and β -blockers ameliorated the atrioventricular conduction blocks thus implicating the excessive parasympathetic tone in neurocardiac dysfunction [51]. This channel was also clinically validated in a SUDEP case affected by epileptic encephalopathy and suspected cardiac dysrhythmias carrying de-novo and novel *KCNA1* intragenic duplication [32].

The Nav1.1 channel role in premature epilepsy mortality was first suspected in the context of a family affected by genetic epilepsy with febrile seizures plus syndrome, recurrent

SUDEP, and a segregating novel, *SCN1A* (I1867T) variant [69]. Subsequently, Le Gal *et al.* [70] reported the first SUDEP case in a genetically confirmed Dravet syndrome. The sudden premature death in Dravet syndrome is currently estimated to affect about 4–12% of children with peak incidence before 4 years of age [71–73]. Moreover, analysis of Dravet syndrome cohort uncovered not only depressed HRV measures [74] but also increased P wave and QT interval dispersion [75]. The *Scn1a*-deficient models reproduced the complex human phenotype with the evidence of spontaneous seizures, autonomic instability, and seizure-driven vagal activation preceding sudden death [76,77]. The administration of parasympatholytics reduced the incidence of ictal bradycardia and SUDEP [77]. A knock-in mouse model of the human mutation *SCN1A-R1407X* [78,79] offered insight into the neurocardiac effects of a patient-specific, disease causing, genetic variant. These mice displayed spontaneous seizures and a prolonged QT interval predisposing to a variety of cardiac dysrhythmias, including ventricular fibrillation and a model SUDEP [78]. Interestingly, the cardiac arrhythmias often preceded the apparent convulsive seizures, thus indicating that *SCN1A* variants might predispose to sudden death through combined neurocardiac or sole cardiac mechanisms [78]. Additionally, there is the experimental evidence that the risk of sudden death in Dravet syndrome may be influenced not only through a gene dosage but also via the affected neuronal cell type and regionally specific differences in *Scn1a* channel brain expression; the selective Nav1.1 deficiency in inhibitory GABAergic neurons resulted in a more severe epileptic phenotype and early and frequent sudden death as compared with mice with constitutive *Scn1a* defect [79]. Also, *Scn1a* deficiency in the forebrain excitatory neurons superimposed upon Nav1.1 defect in inhibitory GABAergic neurons mitigated the seizure phenotype and lessened the incidence of model SUDEP [79].

The discoveries linking *KCNA1* and *SCN1A* to SUDEP brought attention to other epilepsy genes. The *SCN1B* gene encodes a voltage-gated sodium channel β subunit that is critical for proper gating and cell-surface expression of the voltage-gated sodium channel complex [80]. The phenotypic spectrum of *SCN1B* mutations includes genetic epilepsy with febrile seizures plus [81], TLE [82], and Dravet syndrome [83]. Although there has not been a report of human SUDEP linked to *SCN1B*, the *Scn1b* mouse model parallels some of the *Scn1a* animal model features with spontaneous seizures, prolonged QT and RR intervals on the ECG, and early mortality [84,85]. The increasing accessibility of whole-exome profiling facilitated the discovery of a functionally active de-novo variant in yet another epilepsy gene and a candidate SUDEP molecule, the *SCN8A* channel gene, in a child affected by epileptic encephalopathy and SUDEP [86]. Knock-in mouse model carrying the human missense variant p.Asn1768Asp showed early-onset seizures and premature mortality and the age of onset of seizures and death correlated with the mutant gene dosage [87]. The value of translational animal models in pathophysiological analysis of SUDEP was recently validated in the report of the sentrin-specific protease 2 (*SEN2*)-deficient SUDEP mouse model. *SEN2* molecule is a modifier of multiple potassium channels, including the Kv7 channel targeted by the channel opener, the antiepileptic drug, retigabine [88]. The *SEN2*-deficient animal develops epilepsy, vagally driven arrhythmias, and a model SUDEP [88] that were rectified by pretreatment with retigabine [88]. This work showed that the registry of candidate genetic risk factors in premature mortality will likely encompass an

extensive network of interacting proteins, and carefully designed model systems will be invaluable in testing candidate therapeutic interventions.

Recent pilot work on adenosine connection to SUDEP deserves a mention. Adenosine exerts widespread modulatory effects systemically and in the nervous system via four types of guanine nucleotide binding (G) protein-coupled receptors A1, A2A, A2B, and A3 [89]. Seizure triggers a rise in the adenosine level, and the A1 receptors are important in the anticonvulsant and sleep induction effects [89]. However, activation of the adenosine receptors in the brainstem also triggers severe respiratory depression [90[■]]. Preliminary work in a kainic acid seizure model indicated that pretreatment with caffeine, an adenosine receptor antagonist, improved survival in this otherwise lethal pharmacological model of status epilepticus [91]. Although there is insufficient data to draw conclusions regarding adenosine role in SUDEP, this molecular pathway ought to be considered in the candidate pathophysiological molecular network of premature mortality.

Oligogenic predisposition to human sudden unexpected death in epilepsy

There is growing evidence that complex genetic interactions influence the phenotypic expressions of cardiac arrhythmias [92[■]], epilepsy [93–95], and SUDEP [32[■]]. Although *SCN8A* gain-of-function mutations are implicated in epileptic encephalopathies and SUDEP [86,96,97], loss-of-function variants were shown to ameliorate model seizure phenotype [98,99]. Similarly, crossing the *Kcna1* model affected by early-onset severe spontaneous seizures and frequent sudden death with a *Cacna1a* absence seizure model results in a mild seizure phenotype and improved survival [100]. Combined deficiency of the gene *Mapt* encoding microtubule-binding protein τ and *Kcna1* channel results in improvement in seizure frequency, severity, and survival [101[■]]. Similar effect is seen in the *Scn1a/Mapt* digenic model [102]. A human example of genomic complexity in SUDEP was recently illustrated by a pediatric patient who was affected by Dravet syndrome, with severe seizures often accompanied by apnea, and suspected cardiac arrhythmias [32[■]] (Fig. 2). The detailed genomic analysis uncovered complex combinations of single nucleotide polymorphisms and copy number variants in genes expressed in both neurocardiac and respiratory control pathways, including *SCN1A*, *KCNA1*, *RYR3*, and *HTR2C* [32[■]].

CONCLUSION

Our current mechanistic understanding of SUDEP was recently expertly summarized [90[■]]. The lethal trigger might in some individuals be a life threatening cardiac arrhythmia initiated ictally or via a lockstep interictal epileptiform activity. Yet, in others, it may be ictally induced prolonged hypoxemia and hypercapnia resulting in acidosis that aids in seizure termination but at the same time predisposes to bradycardias or asystole in vulnerable individuals [19,90[■]]. The extensive clinical and experimental work has been critical in formulating our current conceptual thinking about SUDEP mechanisms. It has also become evident that the application of currently available diagnostic modalities, such as ECG and respirometry, affords important insight into an individual cardiorespiratory physiology as it may relate to mortality risk assessment. The new cloud computing platforms now permit integration and analysis of large and highly complex physiological data [103],

and are certain to facilitate extraction of physiological SUDEP biomarkers. As indicated by the published data, global molecular profiling in patients with epilepsy will be invaluable in unraveling the individually unique genomic complexities and interactions that underlie the physiological signature of each patient, thus improving the precision of SUDEP risk assessment in the individual. At the same time, sophisticated model systems will be an indispensable tool in the iterative translation of human genetics and physiology as well as in testing pharmacological interventions and preventive interventions. Many essential components for clinically relevant SUDEP research have recently come together as the Center for SUDEP Research (<http://csr.case.edu/>), a National Institute for Neurological Disorders and Stroke (NINDS) funded Center Without Walls for Collaborative Research in the Epilepsies. This unique collaborative network of researchers from the United States and Europe is exceptionally poised for making important discoveries related to SUDEP etiology and individually relevant and quantifiable risk factors, and for prompt clinical application of the findings.

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KEY POINTS

- Cardioautonomic and respiratory dysfunctions have been firmly established as the currently known principal mechanisms leading up to SUDEP.
- Clinical research has shown that comprehensive cardiopulmonary monitoring of patients with epilepsy is critical in understanding candidate pathophysiology of human SUDEP, and it will be important in identifying patients who are likely at increased SUDEP risk.
- Translational animal models have been indispensable in unraveling molecular mechanisms and pathophysiology of the cardioautonomic and respiratory dysfunctions leading to lethal outcome.
- Molecular profiling of human SUDEP cases and the analysis of genetic models have led to the identification of candidate *SUDEP* genes of which most are ion channels active along the neurocardiac, neuroautonomic, and neurorespiratory pathways. However, animal models deficient in *MAPT* and *SEN2* genes have shown that candidate SUDEP molecules will likely involve much larger genic networks.
- Advanced technological platforms have facilitated pilot comprehensive profiling of human SUDEP and aided in uncovering genomic complexities that parallel discoveries in epilepsy by several large-scale efforts.

FIGURE 1.

Example of two patients with SUDEP-onset captured during monitoring in an epilepsy monitoring unit. Of note, visual inspection of video recording together with respiration-induced artifacts on the electroencephalogram were used as surrogate markers of a respiratory effort. Black arrows indicate the early cardiorespiratory collapse observed in all SUDEP cases within the first 3 min postictally leading to immediate death in patient A, whereas in patient G there was a transient and partial restoration of the cardiorespiratory functions until the onset of terminal apnea followed by terminal asystole. SUDEP, sudden unexpected death in epilepsy. Reproduced with permission from [7■■■].

FIGURE 2.

Complex genomic profiles in a SUDEP case affected by Dravet syndrome. The proband harbors an intricate combination of de-novo and inherited variants of variable pathogenic potential in multiple genes of the candidate SUDEP biological pathways. CNV, copy number variant; SNP, single nucleotide polymorphism; SUDEP, sudden unexpected death in epilepsy. Reproduced with permission from [32■].