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It is Premature for a Unified Hypothesis of SUDEP: A Great Amount of Research is Still Needed to Understand the Multi-System Cascade

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Sudden Unexpected Death in Epilepsy (SUDEP) is one of the leading causes of death in people with epilepsy¹. SUDEP accounts for 40% of all epilepsy deaths, with an incidence of 1:1000 patients/year^{1,2}. Many studies have detailed the cascade of multi-system events leading to SUDEP, and identified various initiating triggers and mechanisms²⁻⁵. A recent study in *Epilepsia* by Faingold and Feng⁶ proposes “a unified hypothesis of SUDEP” that centers around seizure-induced respiratory arrest (S-IRA). They propose that seizure-induced adenosine release can cause respiratory depression that ultimately leads to SUDEP, while serotonergic action on the periaqueductal gray (PAG) region of the brainstem promotes autoresuscitation and restorative respiratory responses that could prevent SUDEP. In addition to being leading investigators in this field, the authors masterfully summarize a large body of scientific information on this topic. They provide a comprehensive review of the state-of-the-field regarding S-IRA due to an imbalance between adenosine-mediated depressive vs. serotonin-mediated restorative respiratory responses following a seizure⁶. While the authors acknowledge other proposed mechanisms for SUDEP, the title and major sections of the review indicate that there is a unified hypothesis for SUDEP that is explained by S-IRA.

The prevailing mechanisms for SUDEP include respiratory depression (e.g., S-IRA), laryngospasm-mediated obstructive apnea, post-ictal generalized EEG suppression (PGES), autonomic dysfunction, cardiac arrhythmias, failed arousal, and hemodynamic abnormalities such as cerebral hypoperfusion². These abnormalities collectively contribute to a perfect storm of multi-system dysfunction that ultimately leads to SUDEP. The substrates, triggers, and temporal cascade of cardiorespiratory and autonomic changes likely differ between SUDEP cases.

Peri-ictal central apnea is reported in both humans and animal models^{3,7}. As one justification for focusing primarily on respiration and post-ictal adenosine-related central apnea, the authors refer to the seminal MORETMUS study that reviewed SUDEP cases witnessed in epilepsy

monitoring units⁸. The MORTEMUS study highlights the cascade of multi-system abnormalities leading up to SUDEP. In 67% of the cases, terminal apnea preceded terminal asystole, which the authors cite as evidence of their unified hypothesis. However, the remaining 33% of witnessed cases showed the terminal event was concomitant cardiorespiratory arrest. Moreover, periods of bradycardia and transient asystole preceded terminal apnea in 7 of the 9 subjects for which both respiration and heart rate could be measured. Thus, it is impossible to ignore other contributions to SUDEP based on this study.

Several case series have reported ictal and post-ictal laryngospasm-induced obstructive apnea, with subsequent oxygen desaturation, hypoxemia, and bradycardia with junctional escape beats⁹⁻¹¹. Rodent seizure models also exhibit laryngospasm, with cardiorespiratory dysfunction, and ultimately death^{5,12}. Laryngospasm-mediated obstructive apnea is proposed as a biomarker and inciting event for the multi-system cascade that leads to SUDEP^{5,13}.

PGES is a proposed mechanism of SUDEP in which the attenuation of cerebral activity after the end of a seizure can affect respiratory, cardiac, and autonomic function¹⁴⁻¹⁶. A case-control study of SUDEP cases reported that PGES lasts significantly longer in people with epilepsy that ultimately suffer SUDEP¹⁴. While PGES is thought to be an inhibitory mechanism to protect from recurrent seizures, it could lead to seizure-related pulmonary dysfunction¹⁷, postictal brainstem hypoperfusion¹⁸, and autonomic dysfunction, which would each or collectively increase the risk of sudden death. Furthermore, brainstem spreading depolarization has been shown to lead to both respiratory and cardiac dysfunction¹⁹.

The autonomic nervous system regulates cardiac, respiratory, digestive, and other physiological processes. There is a higher susceptibility to autonomic disturbances in refractory epilepsy, in close temporal relation to seizures, and in SUDEP cases²⁰⁻²⁵. Interictal sympathetic overactivity is seen in most epilepsy²⁶, and decreased vagal function is associated with a higher risk of SUDEP²⁷. Autonomic measures have been shown to be lower in people with Dravet syndrome

compared to healthy controls^{20,28}. Additionally, a recent immunohistochemical analysis reported changes in Acetylcholine (Ach)-related immunoreactivity in a pentylenetetrazol-induced-seizure rodent model²⁹. Combined with the upregulation of Ach-activated Kir3.1 channels and muscarinic Ach receptors in autonomic centers, these abnormalities could be linked to autonomic dysfunction associated with SUDEP²⁹.

Compared to the general population, epilepsy is associated with a 2.8-fold increased risk of cardiac arrhythmias³⁰. The risk is 5.8-fold higher in symptomatic epilepsy, and 66% of sudden cardiac deaths are not temporally linked to seizures³⁰. Epilepsy is associated with chronic cardiac conduction disturbances and altered ventricular repolarization during seizure-free periods, particularly in SUDEP cases^{2,20,28,30-34}. The incidence of ECG abnormalities is higher in intractable forms of epilepsy, surrounding seizures, and in SUDEP cases^{33,35,36}. In people with drug-resistant epilepsy, implantable cardiac monitors detected a high incidence of clinically significant cardiac arrhythmias³⁷. Ictal and post-ictal arrhythmias, such as asystole and ventricular fibrillation, have been reported, some of which are associated with (near) SUDEP³⁸⁻⁴⁰. While the authors discuss the temporal dissociation of cardiac and respiratory dysfunction, these events can arise concurrently as well as one without the other. For example, following a partial seizure a patient developed monomorphic ventricular tachycardia, followed by ventricular fibrillation, which without successful defibrillation would have resulted in SUDEP⁴⁰.

Many genetic forms of epilepsy, especially SUDEP cases, are associated with variants in genes expressed in both the brain and heart⁴¹⁻⁴³. These ion-channelopathies alter electrical function, which provide substrates for SUDEP. Fifteen percent of SUDEP cases have variants in genes linked to cardiac arrhythmias⁴³. Variants in cardiac ion channel genes *KCNH2*, *KCNQ1*, and *SCN5A* traditionally linked to congenital Long QT Syndrome are also associated with epilepsy and SUDEP^{41,43-49}. *KCNA1*, which encodes K_v1.1 potassium channels with predominantly brain-specific expression, can influence cardiac function through autonomic effects⁵⁰.

In a genetic mouse model of Dravet syndrome, *mScn1a* haploinsufficiency paradoxically led to increased cardiac Na^+ current, cardiomyocyte action potential prolongation, myocyte hyperexcitability, re-excitation, increased QT_c duration, non-sinus beats, and reentrant arrhythmias⁴². Ventricular fibrillation was recorded preceding sudden death⁴². Consistent with these results in DS mice, induced pluripotent stem cell derived cardiomyocytes from people with Dravet syndrome also exhibited increased Na^+ current⁵¹. ECG analyses from the person with the largest increase in Na^+ current had cardiac repolarization abnormalities⁵¹. Moreover, a patient with a severe genetic form of developmental epileptic encephalopathy due to a 1.6Mbp deletion in chromosome 2q24 (deletion of many genes including *SCN1A*, *SCN2A*, *SCN3A*, partial *SCN9A*), experienced multiple repeated near-lethal monomorphic ventricular tachycardia arrhythmias⁵². The dynamics of the arrhythmias suggest that it was not secondary to respiratory dysfunction.

The authors' adenosine, serotonin, and PAG hypothesis applies particularly following a generalized tonic-clonic seizure (GTCS)⁶. As the authors note, not all SUDEP cases are temporally linked to a seizure. For example, 54% of SUDEP cases had no GTCS in the month preceding SUDEP, 4% had 0 GTCS/year, and 33% had <10 GTCS/year⁵³. Even when SUDEP is preceded by a seizure, that event is not always a GTCS. Differences in timing of apnea were reported in focal vs. generalized seizures, which could suggest different pathophysiological mechanisms³. Thus, the changes in adenosine levels following a GTCS may explain some, but not all, SUDEP cases.

While there are many animal models of SUDEP, the authors of this review focus extensively on the DBA1/2 rodent models as these satisfy their criteria of 1) consistent and reliable seizure-induced death and 2) the ability for resuscitation. The authors acknowledge that arrhythmias and asystole have been observed in DBA mouse models leading up to sudden death⁵⁴. Other

animal models exist that also fulfill these criteria and provide evidence for other mechanisms of SUDEP that better translate to humans^{42,55,56}.

As mice do not fully recapitulate human neuro-cardiac function^{57,58}, there is a need for new translational models of SUDEP. Recent reports indicate the value of canines, rabbits, and primates for SUDEP research and neurotherapeutics⁵⁹⁻⁶³. Interestingly, like humans, epileptic baboons exhibit cardiac ECG and autonomic abnormalities^{61,62}, and they better reproduce human cardiac electrical function^{64,65}. Additionally, the field is closing in on developing precision medicine to treat genetic epilepsies, which requires the identification of rigorous preclinical animal models with reproducible phenotypes relevant to humans⁶⁶.

The authors propose preventative measures for SUDEP based on evidence that serotonin stimulates autoresuscitation and aids in ending apneic spells. One such suggestion is that the administration of selective serotonin reuptake inhibitors (SSRIs) prevents S-IRA and increases survival following a GTCS⁷. They reference a study by Bateman et al⁶⁷ showing that SSRI improve postictal O₂ saturation; however, this was only seen for focal seizures, and not GTCS, which is the seizure semiology this review focused on regarding S-IRA⁶⁷. Furthermore, SSRIs are associated with a reduced prevalence of ictal, but not post-convulsive central apnea⁶⁸. Their hypothesis is based on results from mouse models, but importantly, a nationwide case-control study in humans showed that SSRIs do not reduce the risk of SUDEP⁶⁹, nor seizure-related and all-cause mortality⁷⁰. In addition to restoring breathing, it is important to monitor and quickly respond to the sudden initiation of lethal ventricular arrhythmias that may or may not be concordant with apnea.

This review proposes that following a GTCS, interaction of adenosine, serotonin, and the PAG can lead to respiratory-driven SUDEP. The study gives the impression that this “unified hypothesis” explains all SUDEP. As epilepsy results in many co-morbidities, we assert that while the proposed sequence of S-IRA is a contributing mechanism, it has yet to be validated as

a unifying hypothesis. As the temporal sequence of multi-system changes differ between SUDEP cases, more information/recordings are needed to develop and validate a unified theory of SUDEP. Due to advances in home monitoring, wearable sensors, research technologies, and the emergence of new translational models of SUDEP, the field is poised to develop a more in-depth knowledge of the mechanisms for SUDEP.

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