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SUDEP: A Local Low Pressure [pO_2] System Makes It Hard to Breathe

Sudden Unexpected Death in Epilepsy Is Prevented by Blocking Postictal Hypoxia

George AG, Farrell JS, Colangeli R, Wall AK, Gom RC, Kesler MT, Rodriguez de la Hoz C, Villa BR, Perera T, Rho JM, Kurrasch D, Teskey GC. *Neuropharmacology*. 2023;231:109513. doi:10.1016/j.neuropharm.2023.109513. PMID: 36948357

Epilepsy is at times a fatal disease. Sudden unexpected death in epilepsy (SUDEP) is the leading cause of epilepsy-related mortality in people with intractable epilepsy and is defined by exclusion; non-accidental, non-toxicologic, and non-anatomic causes of death. While SUDEP often follows a bilateral tonic-clonic seizure, the mechanisms that ultimately lead to terminal apnea and then asystole remain elusive and there is a lack of preventative treatments. Based on the observation that discrete seizures lead to local and postictal vasoconstriction, resulting in hypoperfusion, hypoxia and behavioural disturbances in the forebrain we reasoned those similar mechanisms may play a role in SUDEP when seizures invade the brainstem. Here we tested this neurovascular-based hypothesis of SUDEP in awake non-anesthetized mice by pharmacologically preventing seizure-induced vasoconstriction, with cyclooxygenase-2 or L-type calcium channel antagonists. In both acute and chronic mouse models of seizure-induced premature mortality, ibuprofen and nicardipine extended life while systemic drug levels remained high enough to be effective. We also examined the potential role of spreading depolarization in the acute model of seizure-induced premature mortality. These data provide a proof-of-principle for the neurovascular hypothesis of SUDEP rather than spreading depolarization and the use of currently available drugs to prevent it.

Commentary

A majority of cases of sudden unexpected death in epilepsy (SUDEP) that are clinically witnessed occur shortly after a generalized tonic–clonic seizure. It is unclear why people with epilepsy fail to autoresuscitate from the terminal seizure when they had been able to recover from previous seizures. With this knowledge gap, strategies to prevent SUDEP are lacking. The Mortality in Epilepsy Monitoring Units Study was a large clinical study that revealed important details surrounding witnessed SUDEP events,[1] such as postictal respiration dysfunction and bradyarrhythmia preceded terminal apnea and asystole. With multiple regions in the brainstem working in concert to orchestrate respiration, one line of thought is that dysfunction among this circuitry contributes to terminal apnea. One interesting theory focuses on vasoconstriction-induced hypoperfusion and hypoxia in the brainstem. This idea is supported by the historical observation that respiratory dysfunction, transient apnea, hypoxemia, and hypoxia are associated with seizure semiology; severe seizures can propagate to the brainstem; and cortical seizures cause local ictal-postictal vasoconstriction/hypoperfusion.

It is in this context that George and colleagues[2] took a closer look at hypoxia in the brainstem and asked whether blocking vasoconstriction and subsequent hypoxia could postpone SUDEP in 2 preclinical models. For the acute model, a series of seizures were induced in control mice (ie, with no history of spontaneous recurrent seizures) via intrahippocampal kainate infusion, with the last seizure being terminal. *Kcna1*-null mice were used as the model of chronic epilepsy and SUDEP.[3-7] In the hippocampus and the PreBötzinger Complex, a critical brainstem region for breathing rhythmogenesis, partial pressure of oxygen [pO_2], and electrical activity were monitored, as was heart rate and respiration. After the series of seizures was induced via kainate, the team zoomed in on the sequence of events that followed the terminal seizure to identify what changed first. They reported that the oxygen levels dropped precipitously in the hippocampus and PreBötzinger Complex, and within a few seconds, [pO_2] reached $\sim$4 mm Hg in the PreBötzinger Complex. Then, terminal apnea ensued. This was followed by terminal spreading depolarization (a wave of neuronal silencing) in the brainstem, then asystole.

Previous studies have found that vasoconstriction-induced hypoxia can be blocked with COX1/2 or L-type calcium channel inhibitors[8]; thus, cohorts were pretreated with vehicle, ibuprofen, or nicardipine before seizure induction. Ibuprofen stabilized [pO_2] and postponed hypoxia and death (from

~40 minutes to ~400 minutes). Nicardipine pretreatment yielded similar but less dramatic results. Next, George and colleagues determined whether daily administration influenced longevity in *Kcna1*-null mice and found both ibuprofen and nicardipine significantly increased life span. Overall, this study provides novel evidence for a neurovascular mechanism of SUDEP.

There were many strengths of this study. The first 3 relate to the complementary preclinical models. The induced seizure model allowed the team to control the timing and severity of the seizure. The caveats that the mice do not have epilepsy, nor the associated pathology, were controlled for by using the *Kcna1*-null model. *Kcna1*-null mice have spontaneous seizures that are refractory to anti-seizure drugs, cognitive impairment and cardiac arrhythmias, and 100% mortality rate, modeling multiple aspects of clinical SUDEP.[3-7] Importantly, at the time of sudden death, both models have a generalized tonic–clonic seizure, respiratory dysfunction, and terminal apnea, mimicking the clinically recorded terminal events before SUDEP, and increasing relevance and generalizability.

Additional strengths were in the experimental design. The use of 2 Food and Drug Administration-approved drugs that work via separate mechanisms provided an elegant and potentially translational approach to indirectly examine the neurovascular theory. Furthermore, the study found the effects were dose-dependent, thus increasing validity. Anesthesia influences respiratory centers, and these experiments were conducted in awake, nonanesthetized mice, an important distinction that sets this study apart from previous reports.[9-12]

One limitation of the study was that respiration and heart rate were determined by filtering the raw diaphragmatic electromyographic signal, thus limiting the analyses to the average rate. Nuanced changes in breathing would have provided insight as to whether transient apnea either caused or was indeed a consequence of tissue hypoxia, thus supporting the neurovascular hypoperfusion theory. While the hypoxia was referred to as postictal, the limited analyses did not determine the latency between the end of the seizure and the onset of hypoxia. Brainstem spreading depolarization contributes to sudden death; however, it has been reported to occur both before hypoxia in anesthetized mice, and following hypoxia in both anesthetized and nonanesthetized mice.[2,9,10,12] Whether the varied sequence is a result of the anesthesia or specific to certain types of epilepsy requires further study.

A current limitation in the preclinical SUDEP field is the grey area surrounding the term "seizure bouts" or "clusters." George and colleagues described mice as having at least 2 *bouts* of seizures *with behavioral recovery in between.* The term *behavioral recovery* is key because a similar method is also used to induce status epilepticus,[13] defined as a continuous seizure, or multiple seizures *without recovery* in between, that lasts for more than 5 minutes. Status epilepticus can cause death and is an exclusion criterion for SUDEP. The description of *behavioral recovery between seizures* supports the data's relevance for SUDEP. However, recovery is not defined or quantified and some of the terminal seizures depicted lasted longer than 5 minutes. In these cases, the generated data may apply to status epilepticus. This and other ambiguities are currently being addressed with the SUDEP Task Force, who are systematically identifying SUDEP Common Data Elements to improve translational ease for future research.

This proof-of-concept study prompts additional questions. With cortical hypoxia being more severe following repeated seizures[8] and longer seizures correlating with decreased blood flow,[14] could a difference in seizure history or seizure severity account for the varying degrees of hypoxia and timing of death? COX1/2 has to be blocked *before* the seizure (not during or after) to exert protective effects on oxygen stability[8,14]; could this nuance shed light on why COX1/2 inhibition was unable to *prevent* sudden death?

One clinically significant aspect of this study is that early hypoxia in a key respiratory center supports a neurovascular contribution to terminal apnea and sudden death. The 2021 SUDEP Benchmark Area IVD calls for the identification of preventative strategies. A significant contribution of this study is the transient postponement of sudden death by ibuprofen. Studies have shown hypoperfusion during and after seizures in ictogenic regions, and preclinical data indicate that blocking COX1/2 protects against vasoconstriction for over an hour.[8,14] Thus, the ibuprofen stabilization of [pO_2] in a key respiratory center and continuance of breathing supports the notion that cyclooxygenase-dependent vasoconstrictor prostanoids significantly contribute to brainstem hypoxia in models of sudden death. This study brings us closer to understanding the mechanisms that uniquely permit the last seizure to be terminal; however, as we still are unable to prevent death, further study is required.

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References

1. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units

(MORTEMUS): a retrospective study. *Lancet Neurol*. 2013; 12(10):966-977. doi:10.1016/S1474-4422(13)70214-X. PMID: 24012372.

2. George AG, Farrell JS, Colangeli R, et al. Sudden unexpected death in epilepsy is prevented by blocking postictal hypoxia. *Neuropharmacology*. 2023;231:109513. doi:10.1016/j.neuropharm.2023.109513. PMID: 36948357.
3. Bagnall RD, Crompton DE, Semsarian C. Genetic basis of sudden unexpected death in epilepsy. *Front Neurol*. 2017;8:348. doi:10.3389/fneur.2017.00348. PMID: 28775708; PMCID: PMC5517398.
4. Deodhar M, Matthews SA, Thomas B, et al. Pharmacoresponsiveness of spontaneous recurrent seizures and the comorbid sleep disorder of epileptic Kcna1-null mice. *Eur J Pharmacol*. 2021;913: 174656. doi:10.1016/j.ejphar.2021.174656. PMID: 34838797; PMCID: PMC8787849.
5. 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(15):5167-5175.
6. Iyer SH, Aggarwal A, Warren TJ, et al. Progressive cardiorespiratory dysfunction in Kv1.1 knockout mice may provide temporal biomarkers of pending sudden unexpected death in epilepsy (SUDEP): the contribution of orexin. *Epilepsia*. 2020;61(3): 572-588. doi:10.1111/epi.16434. PMID: 32030748.
7. Iyer SH, Matthews SA, Simeone TA, Maganti R, Simeone KA. Accumulation of rest deficiency precedes sudden death of epileptic Kv1.1 knockout mice, a model of SUDEP. *Epilepsia* 2018;59: 92-105.
8. Tran CHT, George AG, Teskey GC, Gordon GR. Seizures elevate gliovascular unit Ca2+ and cause sustained vasoconstriction. *JCI Insight*. 2020;5(19): e136469. doi:10.1172/jci.insight.136469. PMID: 33004688; PMCID: PMC7566700.
9. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. *Sci Transl Med*. 2015;7(282):282ra46. doi:10.1126/scitranslmed.aaa4050. PMID: 25855492; PMCID: PMC4852131.
10. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. *Nat Med*. 2011;17(4):439-447. doi:10.1038/nm.2333. PMID: 21475241.
11. Dahan A, Teppema LJ. Influence of anaesthesia and analgesia on the control of breathing. *Br J Anaesth*. 2003;91(1):40-49. doi:10.1093/bja/aeg150. PMID: 12821564.
12. Jansen NA, Schenke M, Voskuyl RA, Thijs RD, van den Maagdenberg AMJM, Tolner EA. Apnea associated with brainstem seizures in Cacna1a^{S218L} mice is caused by medullary spreading depolarization. *J Neurosci*. 2019;39(48):9633-9644. doi:10.1523/JNEUROSCI.1713-19.2019. PMID: 31628185; PMCID: PMC6880468.
13. Wolff MD, Farrell JS, Scantlebury MH, Teskey GC. Dynamic oxygen changes during status epilepticus and subsequent endogenous kindling. *Epilepsia*. 2020;61(7):1515-1527. doi:10.1111/epi.16554. PMID: 32478859; PMCID: PMC7496277.
14. Farrell JS, Gaxiola-Valdez I, Wolff MD, et al. Postictal behavioural impairments are due to a severe prolonged hypoperfusion/hypoxia event that is COX-2 dependent. *Elife*. 2016;5: e19352. doi:10.7554/eLife.19352. PMID: 27874832; PMCID: PMC5154758.