Epilepsy Currents
2023, Vol. 23(6) 369-371

DOI: 10.1177/15357597231199340
journals.sagepub.com/home/epi
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A Water Nymph's Curse and the Serotonergic Mechanism of Postictal Breathing Dysfunction

Seizures Cause Prolonged Impairment of Ventilation, CO_2 Chemoreception and Thermoregulation

Teran FA, Sainju RK, Bravo E, Wagnon J, Kim Y, Granner A, Gehlbach BK, Richerson GB. *J Neurosci*. 2023;43(27):4959-4971. doi:10.1523/JNEUROSCI.0450-23.2023. PMID: 37160367

Sudden unexpected death in epilepsy (SUDEP) has been linked to respiratory dysfunction, but the mechanisms underlying this association remain unclear. Here we found that both focal and generalized convulsive seizures (GCSs) in epilepsy patients caused a prolonged decrease in the hypercapnic ventilatory response (HCVR; a measure of respiratory CO_2 chemoreception). We then studied Scn1a R1407X/+ (Dravet syndrome; DS) and Scn8a N1768D/+ (D/+) mice of both sexes, two models of SUDEP, and found that convulsive seizures caused a postictal decrease in ventilation and severely depressed the HCVR in a subset of animals. Those mice with severe postictal depression of the HCVR also exhibited transient postictal hypothermia. A combination of blunted HCVR and abnormal thermoregulation is known to occur with dysfunction of the serotonin (5-hydroxytryptamine; 5-HT) system in mice. Depleting 5-HT with para-chlorophenylalanine (PCPA) mimicked seizure-induced hypoventilation, partially occluded the postictal decrease in the HCVR, exacerbated hypothermia, and increased postictal mortality in DS mice. Conversely, pretreatment with the 5-HT agonist fenfluramine reduced postictal inhibition of the HCVR and hypothermia. These results are consistent with the previous observation that seizures cause transient impairment of serotonergic neuron function, which would be expected to inhibit the many aspects of respiratory control dependent on 5-HT, including baseline ventilation and the HCVR. These results provide a scientific rationale to investigate the interictal and/or postictal HCVR as noninvasive biomarkers for those at high risk of seizure-induced death, and to prevent SUDEP by enhancing postictal 5-HT tone.

Commentary

Many of those in the field of respiratory neurobiology are familiar with the Norse myth "Ondine's Curse" (originally "Undine"; "unda" is Latin for "wave"), the inspiration for the more popular "The Little Mermaid." For those unfamiliar, a popular variant imparts that Ondine, a beautiful and immortal water nymph, falls in love with a mortal man. Although she knows it will cause her to become mortal, age, and die, she weds him after he pledges to love her "with every waking breath." One day, once Ondine has aged out of her youthful beauty, she catches her husband in bed with a mistress and, enraged, she uses the last of her magic to call down a curse that mocks her husband's broken vow: as soon as he falls asleep, he will stop breathing. Inevitably he falls asleep, stops breathing, and dies.

Clinically, Ondine's Curse was first used by Severinghouse and Mitchell to describe patients who had undergone brainstem surgery and lost the ability to breathe during sleep.[1] It has come to describe any condition where breathing ceases or is severely impaired during sleep and has a myriad of causes, including brain damage, tumors, and surgery[2]; the most common cause referred to as congenital central hypoventilation syndrome.

The two most influential drives to breathe are (1) descending inputs originating from forebrain structures and (2) automatic processes originating from brainstem neural circuitry.[3] When descending input is suppressed—as occurs during sleep, anesthesia, and after certain types of seizures—the drive to breathe relies critically on the brainstem's ability to sense and respond to CO_2 levels.[4] This fundamental drive to breathe is referred to as the hypercapnic ventilatory reflex (HCVR). Those with Ondine's Curse cannot adequately regulate breathing in response to elevated CO_2.

Postictal suppression is a well-known phenomenon associated with many types of seizures. Patients are often immobilized, lethargic, and tired. Postictal generalized EEG suppression (PGES) is associated with apnea and the risk of sudden death in epilepsy (SUDEP).[5,6] However, many seizures with extensive PGES and postictal apnea are survived; thus, the inability to recover from postictal apnea is believed to be the final culprit in the cascade of events that leads to SUDEP. Unfortunately, the precise mechanisms of this respiratory dysfunction are entirely unknown and little explored.

Enter Teran and colleagues with their recent publication. In this study, the investigators hypothesize that the CO_2-dependent drive to breathe, the HCVR, is also impaired postictally. They examine the postictal HCVR in patients with epilepsy and 2 mouse models with inducible convulsive seizures.[7] In patients, the HCVR was tested using the rebreathing technique that causes end-tidal CO_2 ($etCO_2$)—an estimate of arterial CO_2—to increase. The HCVR was first tested during the interictal period, and 7 patients were successfully tested in the 2 hours postictal. The HCVR was significantly blunted, with all but one patient experiencing decreased postictal HCVR.

Following up on this striking clinical finding, the authors explored the HCVR in 2 genetic mouse models of epilepsy and SUDEP. Most experiments were carried out in a mouse model of Dravet Syndrome that harbors an R1407X mutation in one Scn1a allele ("$Scn1a^{R1407X/+}$ mice"), which the authors have previously used to demonstrate seizure-induced respiratory arrest as fundamental to SUDEP.[8] Dravet Syndrome patients have haploinsufficiency for the voltage-gated sodium channel NaV1.1, febrile seizures, and a high incidence of SUDEP. The $Scn1a^{R1407X/+}$ mice also have reduced NaV1.1 expression, febrile seizures, and premature mortality via seizure-induced death. Teran and colleagues used standard whole-body plethysmography to test the HCVR in these mice. As with the patients, the HCVR was first tested before any observed seizure occurrence in the mice. Then the mice were heated to produce febrile seizures (Racine Scale 5), and the HCVR was tested again $\sim$15 minutes after seizure termination. Although the interictal HCVR of $Scn1a^{R1407X/+}$ mice was not statistically different than litter mate controls, it was significantly decreased during the postictal period by $\sim$45%, similar to the magnitude observed in patients.

Additionally, the $Scn1a^{R1407X/+}$ mice experienced significant postictal hypothermia proportional to the magnitude of HCVR reduction. However, the authors demonstrate that the decrease in HCVR is not dependent on hypothermia using another transgenic mouse model of epilepsy and SUDEP: mice with a N1768D gain-of-function mutation in a single Scn8a allele ("$Scn8a^{N1768D/+}$ mice"). These $Scn8a^{N1768D/+}$ mice do not have febrile seizures but do have audiogenic seizures.[9] Teran and colleagues demonstrate that after audiogenic seizures, the $Scn8a^{N1768D/+}$ mice experience a minimal drop in core temperature but a substantial postictal inhibition of the HCVR. Thus, confirming that postictal HCVR depression is not dependent on the model used nor core body temperature decrease.

For some time now, serotonin signaling deficiency has been implicated as a mechanism of SUDEP.[10] In addition, serotonergic brainstem neurons contribute to automatic breathing and temperature regulation.[11] Teran and colleagues thus explore the possibility that postictal inhibition of serotonin release explains the decrease in HCVR and body temperature. To this end, they first utilize a tryptophan hydroxylase inhibitor to reduce serotonin levels and observe a drop in body temperature and the HCVR in mice. Conversely, increased serotonin release via administration of FDA-approved fenfluramine mitigates seizure-induced hypothermia and HCVR impairment in the $Scn1a^{R1407X/+}$ mice.

Interestingly, the decrease in postictal HCVR was not experienced consistently across the murine subjects. Some mice experienced no change, or even an increase, in the HCVR; in others the HCVR was virtually ablated. Whether these responses correlated with seizure parameters was not explored, nor was whether altered HCVR was predictive of fatality. Future studies examining these questions, and a more detailed analysis of cellular and molecular mechanisms, will help illuminate possible paths toward novel therapeutic approaches for SUDEP.

In sum, Teran and colleagues have possibly identified another, more common, occurrence of Ondine's Curse. Although postictal suppression is not sleep, it represents an apparent reduction of higher brain activity. Additional loss of CO_2-sensitivity, perhaps by serotonergic neurons, could be the key to seizure fatality that we refer to as SUDEP. It is worth noting that most SUDEP cases occur when a patient is likely asleep (i.e., in bed, during the night). Perhaps the combination of postictal suppression, sleep, and reduced respiratory CO_2-sensitivity is the perfect storm—or hurricane—that drives the most deadly outcome of epilepsy.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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