A Breather for SUDEP

Prevention of Seizure-Induced Sudden Death in a Chronic SUDEP Model by Semichronic Administration of a Selective Serotonin Reuptake Inhibitor.

Faingold CL, Tupal S, Randall M. *Epilepsy & Behavior* 2011;22:186–190.

DBA/1 mice are a chronically susceptible model of sudden unexpected death in epilepsy (SUDEP) that exhibit chronic audiogenic generalized convulsive seizures (GCSs), leading to death from respiratory arrest (RA) if not resuscitated. Serotonin (5-HT) normally enhances respiration in response to elevated CO₂ levels, which occur during GCSs in humans. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine increase 5-HT availability. We examined whether fluoxetine can block GCS-induced sudden death in DBA/1 mice. Fluoxetine (15–70 mg/kg ip) was administered acutely with seizure induction at 30 minutes or semichronically in five daily doses (20 mg/kg/day) with induction after 5 days. Acute fluoxetine (45 or 70 mg/kg) significantly reduced the incidence of RA without blocking seizure susceptibility. Semichronic fluoxetine did not block seizures but significantly reduced seizure-induced RA, which is consistent with effects of SSRIs on respiration in patients with epilepsy [Bateman LM, Li DS, LiN TC, Seyal M. *Epilepsia* 2010;51:2211–4]. These findings suggest that treatment with SSRIs should be evaluated for reducing the incidence of SUDEP in patients.

Commentary

Sudden unexpected death in epilepsy (SUDEP) is a catastrophic event for which persons with epilepsy are at risk; unfortunately, no preventive strategies are available. The risk for SUDEP should not be underestimated, as shown in a recent population-based cohort of children with epilepsy, who were observed for 40 years. In this cohort, SUDEP occurred in 9% of all patients and accounted for 38% of all deaths (1). Although a multitude of risk factors and mechanisms for SUDEP, including cardiac problems, have been discussed, there is growing consensus that respiratory arrest might be the major proximate cause for SUDEP (2). Importantly, respiratory problems were identified in most incidents of SUDEP that were either witnessed or recorded on video EEG, and, frequently, death occurred during sleep and in a prone position (3). In most witnessed or recorded events, sudden death was immediately preceded by a seizure (2, 3). Respiration control via the brainstem depends on the availability of a number of neuroactive substances, such as serotonin (5-HT), adenosine, and endogenous opioid peptides, which are all released during seizures, and whose concentrations are altered during the phase of postictal depression. Two major goals need to be addressed in order to prevent SUDEP in persons with epilepsy: development and characterization of animal models that mimic SUDEP in humans, and development of therapeutic preventative intervention.

Faingold et al. (4) addressed both goals. First, in this (4) and in a previous study (5) the authors used genetically epilepsy-prone DBA mice (DBA/1 and DBA/2). In these animals, audiogenic seizures can easily be triggered at will by the ringing of a doorbell. In both strains of mice, seizures develop with a running phase followed by tonic hind limb extension and respiratory arrest in 88% of animals from the DBA/2 strain (5). Physiologically, and as a response to increased levels of CO₂, 5-HT works on the regulatory network of the brainstem to increase respiration. Previous work from the authors has identified serotonergic deficits as a potential contributing mechanism for SUDEP in audiogenic seizure models (5). By exposing animals to several seizures, in the present study, DBA/1 mice could be conditioned to lethal respiratory arrest in 100% of the population. In contrast to DBA/2 mice, which only have a very narrow developmental time-window of increased (audiogenic) seizure susceptibility, DBA/1 mice are susceptible for several months and therefore constitute a superior model to test chronic therapeutic interventions to prevent SUDEP.

Second, Faingold et al. (4) reasoned that, if SUDEP in their mouse models is due to 5-HT deficiency, then 5-HT augmentation might prevent SUDEP. Pharmacologically, the ambient concentrations of neurotransmitters and neuroactive substances, such as 5-HT, can most effectively be raised by blocking their respective reuptake transporters. Here, the authors used the selective serotonin reuptake inhibitor (SSRI) fluoxetine, which is clinically used to treat major depression. They show that a single acute dose of fluoxetine dose-dependently prevented SUDEP in DBA/1 mice when given 30 minutes prior to the induction of a seizure. Doses of 45 and 70 mg/kg fluoxetine almost completely prevented respiratory arrest and the occurrence of SUDEP, with the higher dose exhibiting additional moderate anticonvulsant

effects. More importantly, a subchronic treatment regimen, in which fluoxetine was administered for 5 days at a dose of 20 mg/kg/day, likewise prevented respiratory arrest and SUDEP with similar effectiveness.

These findings are important and highly translatable. Depression is a comorbid condition of epilepsy and shares several mechanisms, in particular dysfunctional 5-HT homeostasis, with seizures and SUDEP (7). Importantly, the therapeutic use of an antidepressant SSRI, such as fluoxetine or sertraline, in patients with epilepsy might provide dual benefits in ameliorating both the symptoms of depression as well as the risk for SUDEP. In support of this notion, a retrospective study has shown that the use of SSRIs in patients with partial seizures was associated with a reduced likelihood of ictal oxygen desaturation (6). This finding, however, was not typical for secondarily generalized seizures, and additional studies are needed to assess the generality of the potential benefit of SSRIs in the prevention of SUDEP.

Suppression of respiratory function does not seem to be unique to SUDEP. Respiratory suppression with lethal outcome has also been associated with sudden infant death syndrome (SIDS) (7) and with acute lethal outcome after severe traumatic brain injury (TBI) (8). It is intriguing to speculate that those conditions might share common mechanisms. Indeed, both SUDEP and SIDS share common links to 5-HT signaling and respiratory suppression. As is the case in SUDEP, a majority of SIDS infants are found in a prone position, suggesting that 5-HT-dependent mechanisms fail in both conditions, thus avoiding the normal response that leads to arousal and respiratory reactions to hypercapnia and hypoxia. Whereas in SIDS the maturation of 5-HT neurons seems to be impaired, in SUDEP the 5-HT-dependent autoregulatory system in brainstem might transiently be impaired as a consequence of preceding seizure activity.

Although augmentation of 5-HT signaling by use of SSRIs was shown to effectively prevent SUDEP in DBA/1 and DBA/2 mice, it remains to be determined whether these findings can be generalized to other models of SUDEP that are not linked to an inborn genetic defect of 5-HT signaling. Also, 5-HT augmentation might not be the only viable strategy to prevent SUDEP. Of note, impaired adenosine clearance in adenosine kinase-deficient mice has been linked to prolonged periods of respiratory suppression and perinatal death in a possible animal model of SIDS (9). Both seizures and TBI trigger a surge of adenosine, which might suppress respiratory function by overactivation of adenosine receptors in brainstem. Recent studies have shown that a single dose of the adenosine recep-

tor antagonist caffeine, when given after a SUDEP-causing seizure in mice or an otherwise lethal TBI in rats, can prevent respiratory suppression and lethal outcome (8, 10). Together, those studies suggest that SUDEP might be due to a more general disruption of homeostatic metabolic functions, possibly influenced by genetic and epigenetic components, which affect homeostasis and metabolic clearance of important neuroactive molecules in brainstem. Additional understanding of the mechanisms by which epileptic seizures disrupt brainstem homeostasis and control of respiratory functions will allow the development of pharmacologic strategies to prevent SUDEP. As shown here, the use of the antidepressant fluoxetine may be a very feasible approach for the prevention of SUDEP. More safety and feasibility studies are needed to move this promising therapeutic strategy into the realm of clinical applicability.

by Detlev Boison, PhD

References

1. Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. *N Engl J Med* 2010;363:2522–2529.
2. Devinsky O. Sudden, unexpected death in epilepsy. *N Engl J Med* 2011;365:1801–1811.
3. Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: A series of witnessed deaths. *J Neurol Neurosurg Psychiatry* 2000;68:211–213.
4. Faingold CL, Randall M, Tupal S. DBA/1 mice exhibit chronic susceptibility to audiogenic seizures followed by sudden death associated with respiratory arrest. *Epilepsy Behav* 2010;17:436–440.
5. Tupal S, Faingold CL. Evidence supporting a role of serotonin in modulation of sudden death induced by seizures in DBA/2 mice. *Epilepsia* 2006;47:21–26.
6. Bateman LM, Li CS, Lin TC, Seyal M. Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy. *Epilepsia* 2010;51:2211–2214.
7. Richerson GB, Buchanan GF. The serotonin axis: Shared mechanisms in seizures, depression, and SUDEP. *Epilepsia* 2011;52(suppl 1):28–38.
8. Lusardi TA, Lytle NK, Szybala C, Boison D. Caffeine prevents acute mortality after TBI in rats without increased morbidity [published online ahead of print on December 27, 2011]. *Exp Neurol*. doi:10.1016/j.expneurol.2011.12.026.
9. Boison D, Scheurer L, Zumsteg V, Rülcke T, Litynski P, Fowler B, Brandner S, Mohler H. Neonatal hepatic steatosis by disruption of the adenosine kinase gene. *Proc Natl Acad Sci USA* 2002;99:6985–6990.
10. Shen HY, Li T, Boison D. A novel mouse model for sudden unexpected death in epilepsy (SUDEP): Role of impaired adenosine clearance. *Epilepsia* 2010;51:465–468.