Current Literature
In Basic Science

Sudden Unexpected Death in Dravet Syndrome

Sudden Unexpected Death in a Mouse Model of Dravet Syndrome.

Kalume F, Westenbroeck RE, Cheah CS, Yu FH, Oakley JC, Scheuer T, Catterall WA. *J Clin Invest* 2013;123:1798–1808.

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in intractable epilepsies, but physiological mechanisms that lead to SUDEP are unknown. Dravet syndrome (DS) is an infantile-onset intractable epilepsy caused by heterozygous loss-of-function mutations in the *SCN1A* gene, which encodes brain type-I voltage-gated sodium channel $Na_v1.1$. We studied the mechanism of premature death in *Scn1a* heterozygous KO mice and conditional brain- and cardiac-specific KOs. Video monitoring demonstrated that SUDEP occurred immediately following generalized tonic-clonic seizures. A history of multiple seizures was a strong risk factor for SUDEP. Combined video-electroencephalography-electrocardiography revealed suppressed interictal resting heart-rate variability and episodes of ictal bradycardia associated with the tonic phases of generalized tonic-clonic seizures. Prolonged atropine-sensitive ictal bradycardia preceded SUDEP. Similar studies in conditional KO mice demonstrated that brain, but not cardiac, KO of *Scn1a* produced cardiac and SUDEP phenotypes similar to those found in DS mice. Atropine or N-methyl scopolamine treatment reduced the incidence of ictal bradycardia and SUDEP in DS mice. These findings suggest that SUDEP is caused by apparent parasympathetic hyperactivity immediately following tonic–clonic seizures in DS mice, which leads to lethal bradycardia and electrical dysfunction of the ventricle. These results have important implications for prevention of SUDEP in DS patients.

Commentary

Sudden unexpected death in epilepsy (SUDEP) is a rare, fatal complication of epilepsy defined as sudden death in an individual with epilepsy, in the absence of an obvious cause of death (1). The cause of SUDEP is unknown; however, it is hypothesized that there may be a disruption in respiration, heart rhythm, or cerebral shutdown (1). The population incidence of SUDEP in individuals with epilepsy is estimated to be 0.9 per 1,000 in adults and 0.4 per 1,000 in children (2). The risk of SUDEP in children with Dravet syndrome is estimated to be 15-fold greater than other childhood-onset epilepsies, making this a major concern for families and caregivers (3). Dravet syndrome is a severe epileptic encephalopathy that begins in infancy with prolonged hemiclonic or tonic–clonic seizures, often precipitated by fever. As the syndrome progresses, other seizure types emerge along with developmental and cognitive delays, behavioral impairments, and ataxia (4). In more than 80% of cases, Dravet syndrome is caused by mutation of the *SCN1A* gene that encodes the voltage-gated sodium channel $Na_v1.1$ (5). A mouse model of Dravet syndrome was generated by heterozygous deletion of the *Scn1a* gene. This mouse model recapitulates many features of Dravet syndrome, including spontaneous seizures, sensitivity to hyperthermia-induced seizures, cognitive deficits, and ataxia (6–8). Dravet mice also have a high rate of premature death that peaks in the juvenile period between 3–5 weeks of age (6).

In the current study, Kalume and colleagues more fully characterize the premature lethality phenotype in Dravet mice and begin to unravel the underlying mechanism. To more fully understand the relationship between seizures and premature lethality, they used continuous video monitoring during the period of highest lethality risk (postnatal days 23–27). They found a strong correlation between mortality risk and the number of generalized tonic–clonic seizures in the 24 hours preceding death, while the duration of each individual seizure was not correlated. All recorded sudden deaths occurred following a generalized tonic–clonic seizure of relatively short duration. Although they did observe mice that experienced lethal status epilepticus, these were excluded from the study in order to focus on sudden death in Dravet mice as a model of SUDEP in Dravet syndrome patients.

In addition to being expressed in the brain, $Na_v1.1$ is also expressed in the sinoatrial node of the heart, where it contributes to control of heart rate (9). Thus, a key question is whether elevated SUDEP risk in Dravet syndrome results from loss of $Na_v1.1$ function in the central nervous system or heart or both. To address this question, Kalume and colleagues made mice with tissue-specific deletion of $Na_v1.1$ in brain or heart and compared their phenotypes to Dravet mice with $Na_v1.1$ global deletion. Combined video-electroencephalography (EEG) and electrocardiography (ECG) of spontaneous seizures showed episodes of ictal bradycardia during the tonic phase of seizures in mice with global or brain-specific $Na_v1.1$ deletion

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but *not* cardiac-specific deletion. In addition, they observed an increased number of atrioventricular blocks and decreased interictal heart rate variability in mice with global or brain-specific $Na_v1.1$ deletion. Consistent with this, children with Dravet syndrome exhibit decreased heart rate variability compared to age- and sex-matched children with other epilepsy syndromes or with healthy controls (10). This suggests that there may be abnormal regulation of sinoatrial node activity by the autonomic nervous system.

To more systematically examine the basis for sudden death, Kalume and colleagues induced seizures using hyperthermia, a reliable stimulus for seizures in Dravet mice that approximates febrile seizures. Mice with global and brain-specific deletion of $Na_v1.1$ exhibited bradycardia at the beginning of hyperthermia-induced seizures, followed by tachycardia, then bradycardia at the end of seizures. This indicates that there is excessive parasympathetic tone at onset and end of seizures during the tonic phase and increased sympathetic tone during the tonic–clonic phase. The duration of ictal bradycardia was significantly longer in mice that died, suggesting that this may be a critical factor. To probe the relationship of autonomic nervous system function and fatal seizures, they treated the mice with propranolol, which blocks sympathetic signaling; atropine, which blocks parasympathetic signaling; or scopolamine, which blocks peripheral parasympathetic signaling. Treatment with atropine or scopolamine prevented bradycardia and improved survival, while treatment with propanolol was ineffective. This indicates that ictal bradycardia is caused by hyperactivation of parasympathetic input to the heart. This observation suggests that there may be an imbalance in the central homeostatic regulation of autonomic nervous system, similar to the imbalance between excitatory and inhibitory neurotransmission that results in seizures. Further, because this was observed both in mice with global *or* forebrain-specific $Na_v1.1$ deletion, it suggests that this is due to a failure of central regulation of the autonomic nervous system. Consistent with this, there are reports of other dysautonomic symptoms in patients with Dravet syndrome, including difficulty with temperature regulation, sweating and gastric emptying (3).

At this point, it is unclear whether the autonomic nervous system dysfunction and ictal bradycardia are a direct consequence of $Na_v1.1$ deletion or a secondary effect of remodeling of autonomic centers or the cardiac sinoatrial node. Although many features were similar in mice with global and forebrain-specific $Na_v1.1$ deletion, there were also some subtle differences: For example, mice with forebrain-specific $Na_v1.1$ deletion had fatal seizures with bradycardia of shorter duration than mice with global deletion, suggesting that they are somehow less resilient. Further study of the differences between mice with global $Na_v1.1$ deletion and region-specific or temporal-specific deletions may provide clues about the contribution of remodeling to the SUDEP phenotype. Future studies should also include systematic measurement of respiratory function. Another interesting experiment to consider is to induce seizures in mice with cardiac-specific $Na_v1.1$ deletion to examine peri-ictal effects on heart function. Given that these mice are unlikely to have spontaneous seizures that would lead to SUDEP with their lack of brain abnormalities, seizure induction may be necessary to bring out effects of loss of $Na_v1.1$ on the stressed heart.

Although the precise mechanism has yet to be defined, the key finding of this study is the observation that SUDEP risk in mice with $Na_v1.1$ deletion is correlated with profound ictal bradycardia and that limiting the duration of bradycardia via parasympathetic modulation improved survival. This suggests that implantable pacemakers may be an effective treatment for preventing SUDEP in some Dravet syndrome patients, although defining those at particularly high risk remains a significant challenge.

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