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Sudden Unexpected Death in Dravet Syndrome: Respiratory and other physiological Dysfunctions

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Abstract

Sudden Unexpected Deaths in Epilepsy (SUDEP) occur at an alarming higher rate in patients with Dravet syndrome (DS) than in patients with most other forms of epilepsy. DS is a severe infantile-onset epilepsy caused by a heterozygote loss-of-function mutation in *SCN1A*, which encodes the voltage-gated-sodium channel Na_V 1.1. The mechanisms leading to SUDEP in DS or other epilepsies are not completely understood. Understanding the pathophysiological mechanisms of SUDEP, common to most epilepsies and those specific to DS, may pave the way toward the discovery of effective preventive strategies for these epilepsy-related tragic events.

2. Introduction

Sudden unexpected death in epilepsy (SUDEP) is a category of deaths in people with epilepsy that occurs abruptly without warning or other apparent medical causes (Nashef et al., 2012). Epidemiological studies have estimated that such premature deaths occur up to 40 times more frequently in patients with epilepsy than in the general population (Annegers and Coan, 1999; Aurlien et al., 2012; Shorvon and Tomson, 2011). SUDEP is the leading cause of death in patients with intractable epilepsies and accounts for 40–50 % of mortality (Hitiris et al., 2007; Shorvon and Tomson, 2011). Here we review current clinical and experimental data on SUDEP in Dravet Syndrome (DS), an intractable childhood-onset epilepsy with one of the highest rates of such mortality in epilepsy population, and discuss possible implications of respiratory dysfunction in SUDEP mechanisms.

3. Dravet Syndrome

Dravet syndrome (DS) is a life-threatening severe epilepsy with childhood onset, first described by Charlotte Dravet in 1978. It begins in the first year of life, with fever- or temperature-sensitive seizures that often evolve into refractory polymorphic seizures

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including generalized clonic, tonic-clonic, and unilateral seizures. Following the appearance of these seizures, affected children develop several co-morbid conditions including psychomotor regression, ataxia, sleep disturbance, and cognitive impairments, and many die prematurely. DS is therefore considered as an epileptic encephalopathy since it is believed that its seizures are, at least in part, responsible for the multiple comorbid conditions (Dravet et al., 2005; Oguni et al., 2001). Genetic studies have revealed that up to 80% of DS cases is associated with heterozygote loss-of-function mutations in *SCN1A*, the gene that encodes the pore-forming subunit of the type I voltage-gated sodium channels (Na_V 1.1)(Claes et al., 2001; Marini et al., 2007). Over 600 mutations in *SCN1A* have been linked to DS, with 90% of them appearing *de novo*.

Mutant mice carrying a knock-out or knock-in of *Scn1a* are excellent models of this epilepsy, they replicate its main phenotypic characteristics including infantile (P21)-epilepsy onset, high susceptibility to hyperthermia-induced seizures, ataxia, spontaneous seizures, sleep impairments, autistic behaviors, and premature death (Catterall et al., 2010; Oakley et al., 2011; Oakley et al., 2009; Ogiwara et al., 2007; Yu et al., 2006). Studies of these mice led to the discovery of new insights in the pathophysiological mechanisms of DS. Loss of function mutations of *Scn1a* lead to reduced sodium current and action potential firing in GABAergic inhibitory neurons without detectable changes in excitatory neurons in different brain regions. The resulting imbalance between excitation and inhibition likely contributes to brain hyperexcitability, seizures, and co-morbid conditions of DS (Catterall et al., 2010; Oakley et al., 2011). Because SUDEP is an epilepsy-related event, these mouse models are also excellent tools for the search of the pathophysiological mechanisms and preventive remedies of SUDEP in DS.

4. Risks Factors

Studies of the clinical features that contribute to sudden death susceptibility and those of immediate circumstances of deaths in people with various epilepsies have identified several risk factors. These include pharmaco-resistance, increased frequency or recent history of generalized tonic-clonic seizures, lack of treatment with antiepileptic drugs or subtherapeutic levels of drugs, antiepileptic-drug polytherapy (of more than two drugs), frequent changes in antiepileptic drugs, early adulthood, epilepsy of long duration, and mental retardation (Nashef and Ryvlin, 2009; Nobili et al., 2011; Shorvon and Tomson, 2011; Surges et al., 2009). The striking correspondence of these risk factors with the main clinical features of DS suggests a high SUDEP predisposition for patients with this epilepsy. But the relevance of these factors in DS is still under debate considering that they were deduced from studies of patients with diverse types of epilepsies that were poorly defined and most likely did not include a rare epilepsy type such as DS. There are limited data in the literature on SUDEP epidemiology in DS. Studies of mortality restricted to DS patients have indicated that their rate of sudden deaths is remarkably one of the highest in epilepsy population, ranging from 5.7 to 10 % in studied cohorts, and estimated at about 30-fold higher than in patients with other pediatric-onset epilepsies (Akiyama et al., 2010; Dravet et al., 2005; Genton et al., 2011; Sakauchi et al., 2011; Skluzacek et al., 2011). SUDEP is identified as the main cause of fatalities in DS, accounting for up to 60% of them. These fatalities were observed at any age, but the majority of them took place in young adults

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under polytherapy and during sleep (Catarino et al., 2011; Genton et al., 2011). Our recent studies revealed similar distribution pattern of mortality throughout most of the life span of our DS mice (Kalume et al., 2013; Yu et al., 2006). Premature deaths were observed at different age-points from the fourth postnatal week to adulthood (Postnatal week 12), and postnatal week 4 (early adulthood period in mice) was the age-period of peak mortality in these mice (Kalume et al., 2013; Yu et al., 2006). Deaths are observed even in more than 6 month old DS mice in our colony (Unpublished data). In addition, our studies revealed that elevated daily seizure incidence and seizure history are strong risk factors for SUDEP susceptibility in DS mice. The trend of cumulative number of seizures was dramatically elevated in DS mice that died during the fourth postnatal week compared to those that survived (Kalume et al., 2013). Advances in the understanding of genetic epilepsies lead to the hypothesis that mutations in some ion channel genes (such as *SCN1A*) that lead to epilepsy may also constitute a risk factor for SUDEP by causing cardiac or respiratory dysfunctions (Johnson et al., 2009; Nashef et al., 2007). This is consistent with the most common hypotheses of SUDEP mechanisms which suggest that this type of death is due to primary cardiac dysfunctions, respiratory dysfunctions, or cerebral shutdown.

5. Cardiac dysfunctions

Cardiac arrhythmias are common causes for sudden death in the general population and have been suggested as potential risks for SUDEP. Such anomalies are observed during generalized tonic-clonic seizures or focal seizures, especially those involving the temporal lobe or limbic system in humans as well as animals (Devinsky, 2011; Nobili et al., 2011; Surges et al., 2009). They include sinus bradycardia, tachycardia, asystole, premature ventricular or atrial beats, atrioventricular (AV) blocks and AV-nodal escape beats. These arrhythmias can originate from cardiac ion channelopathies or structural abnormalities. Some genes responsible for cardiac channelopathies are expressed in both heart and brain. It has been postulated that their dual expression can lead to potential risk factor for cardiac arrhythmias during seizures and subsequent SUDEP. Dual cardiac and brain expression of *KCNQ1* and *KCNA1* gene which encodes respectively $K_V7.1$ and $K_V1.1$ channels have been reported. $K_V1.1$ homozygous null mice, which exhibit temporal lobe seizures, and $K_V7.1$ mutant mice that carry cardiac long QT syndrome mutations and experience brief partial seizures have been investigated to uncover the cardiac dysfunctions that may underlie SUDEP (Glasscock et al., 2010; Goldman et al., 2009). These two types of mutant mice exhibit interictal and ictal or postictal AV blocks and bradycardia that are sensitive to atropine (Glasscock et al., 2010; Goldman et al., 2009). In $K_V1.1$ homozygous null mice, these cardiac effects are attributed to loss $K_V1.1$ channels in axons of the mutant mice and increase excitability of the vagus nerve. They can also be observed when tested in the presence of a blocker of $K_V1.1$ and $K_V1.2$ channels, in excised nerve preparation (Glasscock et al., 2012). However, some aspects of SUDEP associated with these channel mutations remain unclear. Patients with mutations in $K_V1.1$ channels have cerebellar ataxia, continuous muscle activity, and epilepsy, but do not die of SUDEP. Therefore, the dysfunction of the vagus nerve reported for $K_V1.1$ mutations in mice may not be sufficient tocause SUDEP when $K_V1.1$ mutations are present in patients. Patients and mice with long QT syndrome mutations in $K_V7.1$ channels are thought to die of cardiac arrhythmia, not SUDEP.

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SCN1A, the gene whose mutations have been associated with most cases of DS, is also expressed in both heart and brain. Its product, the Na_V 1.1 channels, participates in the normal function of the two organs (Maier et al., 2003). Our recent studies of SUDEP in *Scn1a* heterozygote knock-out mice revealed suppressed interictal resting heart-rate variability and episodes of ictal bradycardia associated with the tonic phases of generalized tonic-clonic seizures (Kalume et al., 2013). SUDEP occurs immediately following prolonged late ictal-onset bradycardia in these mice. Similar studies in conditional knockout mice demonstrated that specific deletion of Na_V 1.1 channels in forebrain GABAergic interneurons, but not in cardiac myocytes, is sufficient to cause similar cardiac and SUDEP phenotypes as in DS mice. Muscarinic antagonists reduced the incidence of ictal bradycardia and SUDEP in these mice. These findings suggest that SUDEP is caused by apparent parasympathetic hyperactivity initiated near the end of generalized tonic-clonic seizures in DS mice, which leads to lethal bradycardia and electrical dysfunction of the ventricle, followed by cerebral shutdown and death. These results are consistent with findings from studies of autonomic functions in DS patients. Delogu and colleagues found suppressed resting heart rate variability in DS patients compared to other patients or non-epileptic individuals (Delogu et al., 2011). Like in DS mice, most SUDEP cases in patients with DS and other types of epilepsy occur in sleep. Because our studies suggest that bradycardia resulting from apparent hyperactivity of the parasympathetic input to the heart is a critical feature of SUDEP in patients with DS, we postulate that SUDEP might be substantially reduced by use of electrical pacemakers to sustain normal cardiac rhythm through seizures despite the hyperactivation of the parasympathetic nervous system.

Na_V 1.1 channels are abundantly expressed in the brainstem (Allen Brain Atlas, http://mouse.brain-map.org). Our previous studies have shown that loss of Na_V 1.1 channels in DS mice preferentially reduced sodium current and excitability in GABAergic inhibitory neurons of several brain regions (Catterall et al., 2010). Other investigators' studies have shown that GABAergic interneurons from several brainstem nuclei including the rostro-ventral lateral medulla, preBötzinger complex, and nucleus tractus solitarius project to the cardiovagal neurons of the nucleus ambiguus (Frank et al., 2009). Cardiovagal neurons modulate heart rate and heart rate variability. Loss of Na_V 1.1 channels in DS mice could affect the function of these neurons and cause cardiac disturbances that may contribute in the mechanisms of SUDEP in these mice. Our recent findings of suppressed heart rate variability in DS mice is consistent with this prediction. No significant change in heart rate was observed in these mice, possibly due to compensatory mechanisms. However, our findings that specific deletion of Na_V 1.1 channels in forebrain GABAergic interneurons is sufficient to cause SUDEP and that SUDEP can be prevented by block of bradycardia with peripherally restricted muscarinic receptor blocker argue against a primary role for dysfunction of the autonomic nuclei in the brainstem that regulate cardiac and other essential functions in causing SUDEP in DS mice (Kalume et al., 2013). But It will be of interest in future studies to pinpoint the neural circuits that conduct the hyperactivity generated by failure of firing of forebrain GABAergic interneurons downward to the vagal motor nucleus in the brain stem and eventually result in hyperactivity of the parasympathetic nervous system, bradycardia, and death.

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6. Respiratory Dysfunctions

Respiratory dysfunctions have been proposed as a possible cause of SUDEP (Annegers and Coan, 1999; Hitiris et al., 2007; Shorvon and Tomson, 2011; Surges et al., 2009). This idea is based on observations of seizure-associated respiratory difficulties, such as hypoventilation or apnea, in most witnessed SUDEP cases and impaired respiratory function during seizures has been reported in patients who suffered SUDEP (Devinsky, 2011; Langan et al., 2000). In addition, studies have shown that seizures can commonly induce central apnea or hypopnea (Bateman et al., 2008; Nashef et al., 1996; Walker and Fish, 1997). These seizure-induced respiratory dysfunctions were first observed by Hughlings Jackson in 1899 (Jackson, 1899). Experimental studies in sheep have shown that prolonged seizures cause increase in pulmonary vasculature pressure, pulmonary edema, and hypoventilation-associated death (Johnston et al., 1997). In DBA-1 and DBA-2 mice, which are susceptible to audiogenic seizures, respiratory arrest followed by cardiac arrest has been observed prior to seizureinduced deaths (Faingold et al., 2010). Such deaths could be prevented by treatment of the mice with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) (Faingold et al., 2011). But, the potential involvement of respiratory dysfunction in the etiology of SUDEP in DS patients has not been investigated. In DS mice, unlike in audiogenic seizure prone mice, our recent studies showed no visual sign of respiratory arrest prior to SUDEP. Instead, we observed an increase in respiration rate during convulsions and rapid, shallow breathing post-ictally. In future studies, it will be of interest to investigate the changes in respiratory function during SUDEP in DS mice more quantitatively to determine whether physiologically significant changes in respiratory function accompany bradycardia-induced sudden death in DS mice.

As discussed above GABAergic interneurons are located in preBötzinger complex, a brainstem region which is essential for respiratory rhythm generation (Frank et al., 2009). Some investigators have postulated that these GABAergic interneurons of the preBötzinger complex are critically involved in respiratory rhythmogenesis, they are activated in synchrony with inspiration activity (Frank and Mendelowitz, 2012; Kuwana et al., 2006). Others have proposed that these neurons are essential in shaping and assuring the stability of the pattern of respiratory motor output, but not in the generation of rhythm per se (Janczewski et al., 2013). They showed that complete blockade of $GABA_A$ and glycine receptors in preBötzinger andBötzinger complexes did not abolished, but slowed down the respiratory rhythm in anesthetized adult rats. Loss of Na_V 1.1 channels in DS mice could affect their function and cause respiratory impairments that may contribute in the mechanisms of SUDEP in these mice. However, as discussed above our recent findings in mice with specific deletion of Na_V 1.1 channels in forebrain GABAergic interneurons argue against a primary role for dysfunction of the respiratory nuclei in the brainstem in causing SUDEP in DS mice (Kalume et al., 2013). Primary respiratory failure would be accompanied by tachycardia rather than the profound bradycardia that we observe, and lethal sequelae of impaired respiration such as acidosis, hypoxia, and hypercarbia would require longer than the 26-s period of bradycardia that leads to death in DS mice.

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7. Cerebral shutdown

Cerebral shutdown refers to possible scenarios of SUDEP in which the post-ictal seizure suppression causes a substantial generalized cessation of brain electrical activity and subsequently leads to fatal cardiac, respiratory, or arousal response dysfunction. Several case reports of SUDEP, recorded in epilepsy monitoring units or ambulatory settings, have described the cessation of electroencephalographic (EEG) activity preceding a fatal cardiac or respiratory arrest (Bird et al., 1997; Lee, 1998; Lhatoo et al., 2010; McLean and Wimalaratna, 2007; Shorvon and Tomson, 2011; So et al., 2000; Tomson et al., 2008). The authors postulated that cerebral shutdown may be the primary cause of SUDEP in these cases. However, because oxygen saturation was not monitored in these studies, it is still unclear whether hypoxaemia contributed in the mechanisms of these fatalities. One recent retrospective case-control study of people with refractory epilepsy, who underwent pre-surgical monitoring and later died of SUDEP, found that prolonged duration of post-ictal generalized suppression of brain activity was associated with significant increased risk of SUDEP (Lhatoo et al., 2010). However, another similar study did not find such correlation (Surges et al., 2011). Cases of SUDEP with suppression of EEG activity leading to impairments of arousal response have been described in a mouse model of SUDEP with genetically deleted serotonin (5-HT) neurons, which are critical in regulation of breathing and weakfulness (Richerson and Buchanan, 2011). The authors reported that fatal seizures in these mice resulted in failure of recovery from prolonged post-ictal coma. They postulated that this failure of protective arousal mechanisms may make patients susceptible to SUDEP by causing fatal airway obstruction or hypercapnia, similar to that observed in cases of Sudden Infant Death Syndrome (SIDS). Furthermore, it has been proposed that in these circumstances of SUDEP, repositioning or stimulation of the patient by an observer may be an effective preventive approach. None of these scenarios of cerebral shutdown, described above, has been reported in DS patients. In DS mice, a secondary rather than primary, postictal cerebral shutdown was observed during lethal bradycardia. It coincided with the time of cessation of all movements, including respiration (Kalume et al., 2013).

The mechanisms of post-ictal cerebral shutdown are not completely understood. It has been proposed that one mechanism of seizure termination is mediated by endogenous adenosine (During and Spencer, 1992; Lado and Moshe, 2008). This neurotransmitter is released by astrocytes during seizures and has potent anticonvulsant properties (Li et al., 2007; Shen et al., 2010). Studies in mouse models of seizure have shown that adenosine agonists prolonged post-ictal suppression of brain activity. Adenosine receptor blockers are effective in preventing cardiorespiratory dysfunctions and ensuing SUDEP in some mouse models of SUDEP (Boison, 2009; Boison and Stewart, 2009; Shen et al., 2010).

8. Conclusions

The elevated rate of SUDEP in DS than in most other epilepsies is a serious health concern. Respiration dysfunctions have been proposed as a cause for SUDEP in several studies. But their implications in the mechanisms of SUDEP in DS have not been fully investigated. Our recent studies indicate that SUDEP in DS mice is caused by an ictal prolonged bradycardia and associated ventricular electrical dysfunction due to hyperactivity of the parasympathetic

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nervous system. More research is needed to uncover the complete pathophysiological mechanisms and discover preventive strategies for these epilepsy-related tragic events. Considering that SUDEP is an epilepsy-related death and the diversity of epilepsy etiologies, it is likely that the risks factors and mechanisms of SUDEP across epilepsy syndromes are heterogeneous.

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Highlights

Dravet syndrome is an epilepsy subtype with one of the highest rates of sudden unexpected death.

We reviewed current data on sudden unexpected deaths in Dravet syndrome and other epilepsies.

We discussed the physiological changes that may lead to these types of death in Dravet syndrome.

More research is needed to completely uncover the multiples causes of these deaths.

This will help in the search for preventive strategies of these fatalities in Dravet syndrome and other epilepsies.