**Note to reader**: This is the introduction of a manuscript titled “Time of day and a ketogenic diet influence susceptibility to SUDEP in *Scn1a R1407X/+* mice”. This was submitted but will likely bounce back with a bunch of reviewers’ comments. I wanted to take this opportunity to revisit my introduction and make sure it makes sense to the reader in terms of content and flow. I’m only including the abstract here for those that want more context, so don’t feel like you have to revise it. Thank you for your thoughtful feedback!

**Abstract**

Sudden unexpected death in epilepsy (SUDEP) is a major cause of mortality in patients with drug-resistant epilepsy. Most SUDEP cases occur in bed at night and are preceded by a generalized tonic-clonic seizure (GTCS) and. Dravet syndrome (DS) is a severe childhood-onset epilepsy commonly caused by mutations in the *SCN1A* gene. Affected individuals suffer from refractory seizures and an increased risk of SUDEP. Here, we demonstrate that mice with the *Scn1aR1407X/+* loss-of-function mutation experience more spontaneous seizures and SUDEP during the early night. In DS mice we evaluate effects of long-term ketogenic diet (KD) treatment on mortality and seizure frequency. DS mice showed high premature mortality (44% survival by P60) that was associated with increased spontaneous GTCSs 1-2 days prior to death. KD treated mice had a significant reduction in mortality (86% survival by P60) compared to mice fed a control diet. Interestingly, increased survival was not associated with decreased spontaneous non-fatal seizures. Further studies are needed to determine how KD confers protection from SUDEP. Moreover, our findings implicate time of day as a factor influencing the occurrence of seizures and SUDEP. DS mice, though nocturnal, are more likely to have SUDEP at night, suggesting that the increased incidence of SUDEP at night in DS mice may not be solely due to sleep.

**INTRODUCTION**

Sudden unexpected death in epilepsy (SUDEP) is estimated to occur in ~17% of patients with epilepsy1. This number can drastically increase to 50% in patients with poorly controlled and severe epilepsy2. Although the mechanisms underlying SUDEP are not fully understood, an increasing body of evidence suggests SUDEP is due to seizure-induced cardiorespiratory dysfunction3,4. However, little is known about the circumstances leading up to SUDEP. A strong association with sleep has been documented in a number of studies3,5. Although a significant majority of patients are found in bed in the prone position at the time of death6-8, the occurrence of SUDEP during sleep varies widely among published case studies9. This suggests that other circadian factors may be relevant.

Dravet Syndrome(DS) is a devastating epileptic encephalopathy of childhood-onset that typically manifests as febrile seizures in the first year of life and progresses to refractory epilepsy10. Children with DS develop several comorbidities, such as ataxia, sleep disturbance and cognitive impairments11. In patients with DS, the risk of SUDEP is estimated to be 15 times higher than in other pediatric epilepsies. Premature death occurs in 21% of DS patients, with SUDEP accounting for nearly half of these deaths12. Approximately 85% of DS cases are caused by dominant loss-of-function mutations of the *SCN1A* gene, which encodes the neuronal voltage-gated sodium channel Nav1.111,13. DS mouse models have proven to be an efficient research tool for understanding the pathophysiology of SUDEP as they recapitulate many aspects of the clinical condition: they have spontaneous seizures and a high incidence of premature mortality14. They also display impaired sleep architecture homeostasis10.

A recent study found that time of day can have an independent influence on physiological changes associated with a seizure, particularly breathing15. This is important as seizure-induced changes in respiratory physiology contribute to SUDEP in patients3,16-22 and in DS mice14. In the present study, we aimed to determine in DS mice whether: 1) spontaneous seizures and SUDEP are more likely to occur in the light or dark phase; 2) seizure frequency changes in the days prior to SUDEP; and 3) treatment with a high-fat, low-carbohydrate ketogenic diet (KD), which has been proven to be protective in other seizure models23,24, results in fewer spontaneous seizures and death.