Childhood absence epilepsy, the most common form of pediatric epilepsy, is emerging as a target of heightened clinical concern[1-4]. It predominantly affects young children, peaking at ~6 years of age[5], and is characterized by frequent, generalized, brief seizures associated with the loss of consciousness. In 2013, the first drug study performed in accordance with International League Against Epilepsy (ILAE) standards concluded that current anti-seizure drugs fail to treat more than half of patients with childhood absence epilepsy[1]. Considering its many comorbidities[4,6], as well as the greater risk of developing other seizure disorders when absence seizures are not controlled[7,8], it is imperative that we have better available treatments. This application addresses this urgent need.

While seizures are spontaneous events, environmental factors such as diet[9-15] modulate their occurrence. Recently, in a rodent model of absence epilepsy, we have learned that brief episodes of food deprivation can nearly double the occurrence of seizures[13]. This observation is particularly compelling in light of new work demonstrating that a slight drop (~25%) in blood glucose levels selectively activates neuronal activity in the human thalamus[16-18], the brain structure most intimately associated with the generation of absence seizures[19-21]. Together, these findings warrant deeper investigation, as the underlying mechanisms offset the actions of anti-seizure drugs and thus amplify treatment failures. Indeed, a recent report suggests that strict glucose control in patients with absence seizures may provide beneficial, adjunct therapeutic effects[13].

We propose to examine how acute dietary changes modulate neural circuits in the rodent thalamus to exacerbate seizures. Our data suggest that reduced levels of blood glucose increase the occurrence of absence seizures. The central goal guiding this proposal is to determine the mechanisms by which seizure exacerbation occurs. *We approach this goal with the overarching hypothesis that glucose directly modulates neural circuits in the thalamus to exacerbate seizures.* The following Specific Aims (**Fig. 1**) test this hypothesis:

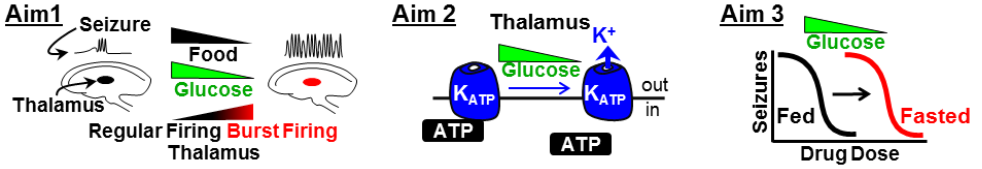

Figure 1. Specific Aims. Aim 1. Low glucose increases seizures. **Aim 2.** Low glucose activates K_{ATP} channels in the thalamus. **Aim 3.** Low glucose reduces anti-absence seizure drug efficacy.

Specific Aim 1

Hypothesis: Low blood sugar is the primary trigger for elevated absence seizures during acute fasting.
Rationale: Our data from two rodent models of absence epilepsy demonstrate that fasting-induced seizures are associated with changes in levels of both glucose and ketone bodies in the blood. The latter serve as energy substrates during periods of low glucose and are hypothesized to modulate seizures[22,23]. However, our preliminary data indicate that absence seizures are triggered specifically by low blood glucose and not by alternative energy substrates. We propose that low blood glucose specifically targets the thalamus, overriding a critical inhibitory brake ("choke-point") that restrains absence seizures[24].
Approach: Video-EEG will measure seizure occurrence in rodents during (a) global hypoglycemia and (b) restricted hypoglycemia targeted to the thalamus. *In vivo* calcium imaging techniques and depth electrodes will specifically assess the involvement of thalamic circuits during glucose-modulated seizures.

Specific Aim 2

Hypothesis: ATP-dependent potassium channels confer thalamocortical neurons with glucose sensitivity.
Rationale: Repetitive burst firing by thalamic neurons underlies absence seizure generation[19,20,25]. We propose that low glucose promotes thalamic burst firing by activating ATP-dependent potassium (K_{ATP}) channels.
Approach: Electrophysiological approaches in acute brain slices will assess glucose sensitivity of thalamic tissue both at the cellular and the network level. Anatomical, biochemical, molecular and electrophysiological assays will establish K_{ATP} channel expression levels and functionality in the thalamus. Electrophysiological and pharmacological assays will assess interaction between glucose and K_{ATP} channels in thalamic tissue.

Specific Aim 3

Hypothesis: Diet modulates the effectiveness of anti-absence seizure drugs.
Rationale: Anti-absence seizure drugs are presumed to reduce seizures by dampening ictogenic mechanisms in the thalamus (e.g. ethosuximide). We propose that fasting counteracts anti-seizure drugs by promoting pro-seizure mechanisms. On balance, seizures persist despite pharmacological treatment.
Approach: Anti-seizure drug effectiveness will be assessed in rodents before and after changes in diet.

In sum, this proposal pursues ictogenic mechanisms with the understanding that the brain is an incredibly metabolically-demanding organ. Recognizing that epileptic seizures are complex, probabilistic events[26,27] whose expression is regulated by external factors such as diet will critically inform treatment strategies. Herein, we apply these principles towards the most common form of pediatric epilepsy.