Online Proceedings

POSTER SESSION 3

MGH 241, Easel 141

2:30 PM to 4:00 PM

Influence of Cardiorespiratory Coupling on the Risk of Sudden Unexpected Death in a Mouse Model of Dravet Syndrome

Sandy Liang, Senior, Biology (Molecular, Cellular & Developmental)
Mentor: Franck Kalume, Neurological Surgery and Pharmacology, UW/ Seattle Children's

Sudden unexpected death in epilepsy (SUDEP) is the most common type of death in people with intractable epilepsies, including Dravet syndrome (DS). DS is a treatment-resistant infantile-onset epilepsy syndrome with comorbidities of cognitive impairment and premature death. DS is caused by a heterozygous loss-of-function mutation in SCN1A, the gene encoding the α subunit of the type I voltage-gated sodium channel $Na_v1.1$. Cardiovascular dysfunctions have been identified as the main causes of SUDEP. Recent studies have indicated that changes in cardiorespiratory coupling can indicate signs of disease and predict disease susceptibility, such as schizophrenia. We used the established mouse model of DS, which carries a global knock out of Scn1a, and conducted an examination of cardiac and respiratory functions. We recorded video recordings, electroencephalogram (EEG), electrocardiogram (ECC), whole body plethysmography, and LabChart Software 8.0 (AD Instruments) in freely moving DS and wild type (WT) control mice. We then identified and characterized the defects in cardiorespiratory coupling strength associated with SUDEP risk in the DS mice. We hypothesize that cardiorespiratory coupling of DS mice, compared to the WT mice, is disturbed and results in increased complexity between the heart rate and respiration. Findings from these studies may indicate that cardiorespiratory coupling parameters can be used as biomarkers of susceptibility to sudden death in intractable epilepsies and in other severe neurological disorders.

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***c-Fos* Studies in a Mouse Model of Leigh Syndrome**

Jennifer Wong, Senior, Biology (Physiology)
Mentor: Franck Kalume, Neurological Surgery and Pharmacology, UW/ Seattle Children's

Leigh syndrome (LS) is an infantile necrotizing brain disorder associated with progressive neurological deterioration of the central nervous system (CNS), and is caused by the loss of *Ndufs4*. The *Ndufs4* gene codes for the iron-sulfur protein 4 subunit of Complex I (NADH dehydrogenase) in the electron transport chain. The absence of *Ndufs4* causes deficiency in Complex I, which negatively impacts mitochondrial energy production and results in symptoms associated with LS. One of the symptoms LS patients experience is seizure activity. Seizures can be caused by inhibition of inhibitory neurons, resulting in hyperexcitibility of neurons. In this study, we sought to identify brain regions that are involved in the generation of seizure activity in a mouse model of LS using *c-Fos* immunocytochemistry. *c-Fos* proteins are activated by seizures, and therefore are treated as metabolic markers for tracking seizure pathways. The LS mouse model used is homozygous (Hmz) Ndufs-floxed crossed with Gad-Cre mice, which selectively removes the *Ndufs4* gene in GABAergic inhibitory interneurons. We induce thermal seizures in LS mice using a heating lamp. Sham animals, of the same corresponding genotype, are processed in the same protocol but are not exposed to the heating lamp. The mice are perfused 90 minutes after the start of seizure activity, and the brain tissues are extracted and fixed with PFA. Fixed brains are sliced, and the slices are stained and imaged on a confocal microscope to map out sites of *c-Fos* immunoreactivity. We anticipate that our results will show that Hmz Ndufs/Gad-Cre(+) mice with thermal-induced seizures will express elevated levels of *c-Fos* in the hippocampus, thalamus, and cortex. The results will provide insights on potential treatment drugs targeted at these specific brain regions in LS patients.