Plan Overview

A Data Management Plan created using DMPTool

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Title: Regulation of Zn2+ translocation through the mitochondrial Ca2+ uniporter (MCU) and ischemic brain injury

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Project abstract:

Transient brain ischemia results in delayed neuronal injury hours and days later. Mitochondrial dysfunction appears to be a critical mechanism in the development of such delayed ischemic injury. Additionally, considerable evidence points to a crucial role for Zn2+ ions. Upon ischemia, labile Zn2+ ions accumulate in many cerebral neurons, due to a combination of synaptic Zn2+ influx at postsynaptic sites and Zn2+ release from intracellular stores. ***Importantly, Zn2+ chelators have shown protective efficacy in both*** **in vitro** ***and*** **in vivo** ***models of stroke, implicating Zn2+ as an important contributor to ischemic neuronal injury***. However, despite many studies having examined effects of Zn2+ in neuronal preparations, mechanisms through which Zn2+ contributes to *ischemic* injury remain poorly understood. Some neurons including CA1 pyramidal neurons are especially vulnerable to brain ischemia while others, including CA3 neurons are more resistant. Using a hippocampal slice model of transient brain ischemia, we found delayed and prolonged mitochondrial Zn2+ accumulation to occur in CA1 but not in CA3 neurons. We also found that this Zn2+ enters mitochondria through the mitochondrial Ca2+ uniporter (MCU), and results, after several hours, in persistent mitochondrial depolarization and swelling. ***We hypothesize that this delayed mitochondrial Zn2+ accumulation may provide an attractive target for beneficial therapeutic interventions that could be delivered after a period of transient ischemia.*** However all existent MCU blockers also inhibit Ca2+ accumulation to mitochondria. Thus understanding the specific mechanisms leading to Zn2+ accumulation into mitochondria and isolating them from those of Ca2+ is needed. Recent studies indicate that Ca2+ ions directly regulate the gating of the MCU by direct binding to associated subunits, which are differentially expressed between CA1 and CA3 neurons. Whereas Zn2+ entry through the MCU appears to be promoted by cytosolic Ca2+ rises, specific mechanisms of Zn2+ entry through the channel have not been studied. AIM 1 will use cultured neurons to investigate ways in which intracellular Ca2+ and Zn2+ levels may act to regulate Zn2+ uptake into mitochondria. Studies in AIM 2 will employ knockdown or overexpression of MCU associated subunits to examine how mitochondrial Zn2+ uptake depends upon the differential expression of MCU complex subunits. AIM 3 will use the in vitro acute

hippocampal slice ischemia model to investigate how the subunit composition of the MCU complex contributes to prolonged Zn2+ accumulation in CA1 mitochondria after ischemia and assess differences from CA3. This aim seeks to determine the basis of the selective prolonged Zn2+ accumulation in CA1 neurons. The broad goal of this study is to investigate how mechanisms of mitochondrial Zn2+ accumulation can be discriminated from those of Ca2+ in order to selectively target this deleterious Zn2+ accumulation after ischemia.

Start date: 12-01-2023

End date: 11-30-2025

Last modified: 01-19-2024

Copyright information:

Regulation of Zn2+ translocation through the mitochondrial Ca2+ uniporter (MCU) and ischemic brain injury

The project will generate calcium and zinc imaging data from ~200 mouse cortical neuronal cultures and from ~ 100 mouse brain slices. generating~1000 datasets totaling approximately 1 TB in size. The data will be processed to calculate relative cytosolic and mitochondrial calcium and zinc levels and the subsequent data set used for statistical analysis. The project will also generate genetic (RNA seq) and immunocytochemical data pertaining as to relative expression levels of MCU associated peptides in murine CA1 vs CA3 pyramidal neurons. This data will be from ~ 20 mice and will be less that 100 MB.

All data produced in the course of the project will be preserved and shared.

To facilitate interpretation of the data, *metadata, and statistical analysis plans* will be created, shared, and associated with the relevant datasets.

data will be made available in *txt and jpg* format and will not require the use of specialized tools to be accessed or manipulated.

Data will be stored in common and open formats, such as jpg for our image data, and txt for analyzed values.

All dataset(s) that can be shared will be deposited in Dryad or Zenodo

Dryad provides searchable study-level metadata for dataset discovery. Dryad assigns DOIs as persistent identifiers, and has a robust preservation plan to ensure long-term access. Data will be discoverable online through standard web search of the study-level metadata as well as the persistent pointer from the DOI to the dataset.

All scientific data generated from this project will be made available as soon as possible, and no later than the time of publication or the end of the funding period, whichever comes first. The duration of preservation and sharing of the data will be a minimum of 10 years after the funding period.

There are no anticipated factors or limitations that will affect the access, distribution or reuse of the scientific data generated by the proposal.

Controlled access will not be used. The data that is shared will be shared by unrestricted download.

Question not answered.

Lead PI John Weiss, ORCID: 0000-0001-9323-7813, will be responsible for the day-to-day oversight of lab/team data management activities and data sharing. Broader issues of DMS Plan compliance oversight and reporting will be handled by the PI and Co-I team as part of general UCI stewardship, reporting, and compliance processes.
