

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

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

Data Type

Types and amount of scientific data expected to be generated in the project: *Summarize the types and estimated amount of scientific data expected to be generated in the project.*

Describe data in general terms that address the type and amount/size of scientific data expected to be collected and used in the project (e.g., 256-channel EEG data and fMRI images from ~50 research participants). Descriptions may indicate the data modality (e.g., imaging, genomic, mobile, survey), level of aggregation (e.g., individual, aggregated, summarized), and/or the degree of data processing that has occurred (i.e., how raw or processed the data will be)

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 than 100 MB.

Scientific data that will be preserved and shared, and the rationale for doing so: *Describe which scientific data from the project will be preserved and shared and provide the rationale for this decision.*

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

Metadata, other relevant data, and associated documentation: Briefly list the metadata, other relevant data, and any associated documentation (e.g., study protocols and data collection instruments) that will be made accessible to facilitate interpretation of the scientific data.

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

Related Tools, Software and/or Code

State whether specialized tools, software, and/or code are needed to access or manipulate shared scientific data, and if so, provide the name(s) of the needed tool(s) and software and specify how they can be accessed.

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

Standards

State what common data standards will be applied to the scientific data and associated metadata to enable interoperability of datasets and resources, and provide the name(s) of the data standards that will be applied and describe how these data standards will be applied to the scientific data generated by the research proposed in this project. If applicable, indicate that no consensus standards exist

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

Data Preservation, Access, and Associated Timelines

Repository where scientific data and metadata will be archived: Provide the name of the repository(ies) where scientific data and metadata arising from the project will be archived; see [Selecting a Data Repository](#)

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

How scientific data will be findable and identifiable: Describe how the scientific data will be findable and identifiable, i.e., via a persistent unique identifier or other standard indexing tools.

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.

When and how long the scientific data will be made available: Describe when the scientific

data will be made available to other users (i.e., no later than time of an associated publication or end of the performance period, whichever comes first) and for how long data will be available.

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.

Access, Distribution, or Reuse Considerations

Factors affecting subsequent access, distribution, or reuse of scientific data: NIH expects that in drafting Plans, researchers maximize the appropriate sharing of scientific data. Describe and justify any applicable factors or data use limitations affecting subsequent access, distribution, or reuse of scientific data related to informed consent, privacy and confidentiality protections, and any other considerations that may limit the extent of data sharing. See [Frequently Asked Questions](#) for examples of justifiable reasons for limiting sharing of data.

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

Whether access to scientific data will be controlled: State whether access to the scientific data will be controlled (i.e., made available by a data repository only after approval).

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

Protections for privacy, rights, and confidentiality of human research participants: If generating scientific data derived from humans, describe how the privacy, rights, and confidentiality of human research participants will be protected (e.g., through de-identification, Certificates of Confidentiality, and other protective measures).

Question not answered.

Oversight of Data Management and Sharing

Describe how compliance with this Plan will be monitored and managed, frequency of oversight, and by whom at your institution (e.g., titles, roles).

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.
