Photoacoustic Microscopy of Metabolic Dysfunction in Alzheimer’s Disease

https://neurodegenerationresearch.eu/survey/photoacoustic-microscopy-of-metabolic-dysfunction-in-alzheimer%c2%92s-disease/

Principal Investigators

HU, SONG

Institution

UNIVERSITY OF VIRGINIA

Contact information of lead PI
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Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a leading cause of adult disability and the most common cause of dementia in the United States. Although tremendous efforts have focused on understanding AD, no cure has been found. Current therapies that target the central nervous system show limited efficacy. Emerging evidence suggests a

synergistic effect between AD pathology and the coexisting dysfunction in cerebral metabolism. However, it is still uncertain whether the metabolic dysfunction is an underlying cause or merely a consequence of disease. Answering this question may shed light on new and hopefully more effective therapies that target disrupted metabolic pathways in AD. Examining the causality between metabolic dysfunction and AD pathology requires a technique capable of spatiotemporally imaging both cerebral metabolism and the deposition of amyloid plaques-a key pathological hallmark of AD. Positron emission tomography (PET) can carry out this task in the clinic; however, the initial stage of plaque deposition is largely asymptomatic and thus difficult to capture in patients. Mouse models that recapitulate AD pathology through established genetic alterations are ideally suited for this mechanistic study, because they have documented timelines of plaque development. Moreover, focal ischemia in mouse AD models can trigger rapid seeding of amyloid plaques in the ischemic cortex, in contrast to the spontaneous seeding on the contralateral side. This paradigm offers a unique opportunity to study the relationship between metabolism dysfunction and AD pathology in both induced and spontaneous plaque development in the same mouse. Although exciting, imaging the appearance of individual plaques and the disruption of local cerebral metabolism in mice requires high spatial resolution far beyond that of PET. Photoacoustic microscopy (PAM) holds great potential to meet this technical demand. In the proposed research, a novel dichroism contrast will be developed to enable high-contrast PAM of individual amyloid plaques through the intact mouse skull. In parallel, a new methodology will be established to derive total concentration of hemoglobin, oxygen saturation of hemoglobin, oxygen extraction fraction, and cerebral blood flow at the tissue level in the AD mouse brain. With the four tissue- level measurements, the cerebral metabolic rate of oxygen-a gold-standard metabolic index-can be computed at the microscopic level. Integrating the amyloid and metabolic contrasts into an unprecedented PAM platform will ultimately enable us to image AD pathology and metabolic dysfunction at the same spatiotemporal scale. The co-evolution of CMRO2 and amyloid aggregation acquired by PAM in the mouse AD-ischemia model would otherwise be impossible to obtain with agglomerated observations from a collection of different imaging techniques operating at different spatiotemporal scales. This technical innovation will open a new avenue for mechanistic studies of the disrupted metabolic pathways in AD, which may lead to novel and promising therapies.

Further information available at:

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