A Novel Role for Very Long Chain Fatty Acids in Brain Function

Blake R. HOPIAVUORI[1,3,4], Martin-Paul AGBAGA[1,3,4,5], Joseph WILKERSON[3,4,5], Richard S. BRUSH[4], Andria F. HEDRICK[2,3], Debra SAUNDERS[7], Faizah BHATTI[3,4,8], Nawajes A. MANDAL[1,3,4,5], Luke SZWEDA[6], Vibhudutta AWASTHI[2,3], Rheal TOWNER[1,7], Robert E. ANDERSON[1,3,4,5]

[1]Oklahoma Center for Neuroscience, [2]Department of Pharmaceutical Sciences, [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]Department of Ophthalmology, Dean McGee Eye Institute, [5]Department of Cell Biology, University of Oklahoma Health Sciences Center, [6]Free Radical Biology and Aging Research Program, Oklahoma Medical Research Foundation, [7]Advanced Magnetic Resonance Center, Oklahoma Medical Research

Purpose: ELOngation of VeryLong chain fatty acids-4 (ELOVL4) is an elongase responsible for biosynthesis of very long chain (VLC; ≥C28) fatty acids, found as components of complex lipid molecules. ELOVL4 synthesizes the VLC polyunsaturated fatty acids (VLC-PUFA) in retina and testes, and VLC saturated fatty acids (VLC-FA) in skin and brain. A 2011 case study reported that homozygous inheritance of the Stargardt's (STGD3) mutation in ELOVL4 causes a central nervous system (CNS) phenotype in humans, including seizures, intellectual disability, spastic quadriplegia and death. We hypothesize that ELOVL4-synthesized VLC-FA play an essential role in neural cell structure and function.

Methods: We generated the first successful animal model for STGD3/STGD3 inheritance. ELOVL4 localization within the CNS was determined using immunofluorescence. Brain lipids were extracted from hippocampusand separated by solid phase extraction (SPE) before GC/MS analysis. Positron emission tomography (PET) was used to assess CNS uptake of fluorodeoxyglucose (FDG) in STGD3/STGD3 mice. HPLC was used to assess intermediary metabolism in STGD3/STGD3 mice. Membrane fractionation was performed on baboon hippocampus to isolate synaptic membranes for lipid analysis.

Results: Our STGD3/STGD3 mice recapitulate the human phenotype, developing seizures at P19 followed by death at P21. Immunofluorescence showed the highest enzyme immunoreactivity within the hippocampus, in neurons of the dentate gyrus. GC/MS confirmed the presence of 28:0 and 30:0 in sphingolipids. PET imaging of STGD3/STGD3 mice revealed a 3-fold increase in the amount of FDG uptake into the CNS. Metabolomic analysis revealed significant increases in ATP levels in STGD3/STGD3 mice. Membrane fractionation revealed enrichment of 28:0 and 30:0, but not VLC-PUFA, in synaptic vesicle membranes.

Conclusions: This is the first study to demonstrate mutations in Elovl4 causing a CNS phenotype in an animal model, implicating for the first time a potential role of VLC-FA in neural cell structure and function.