MECHANISMS OF AGE-RELATED COGNITIVE DYSFUNCTION: ROLE FOR ASTROCYTE METABOLISM

S Logan[1,2,3], and W E. Sonntag[1,2,3]

[1]Department of Rehabilitation Sciences, College of Allied Health
[2]Oklahoma Center for Geroscience and Healthy Brain Aging,
Department of Biochemistry and Molecular Biology,
[3]Oklahoma Center for Neuroscience,
University of Oklahoma Health Sciences Center

Background: Cognitive decline is a debilitating aspect of aging and neurodegenerative diseases such as Alzheimer's disease that is closely associated with mitochondrial dysfunction, increased oxidative stress and a concomitant reduction in circulating levels of insulin-like growth factor-1 (IGF-1). Reactive astrocytes play an integral role in the maintenance and modulation of neuronal health and function by supplying energy substrates, trophic factors, such as IGF-1, and facilitate glutamate and Aβ clearance necessary for neuroprotection and neurotransmission.
Purpose: The purpose of this study was to investigate the effect of the decline in IGF-1 signaling on brain mitochondrial metabolism and astrocyte function and its association with learning and memory.
Methods: We reduced circulating levels of IGF-1 by AAV mediated knockdown of liver IGF-1 in *Igf1*$^{f/f}$ mice (LID). Learning and memory was assessed using the radial arm water maze in young and old mice as well as tamoxifen-inducible astrocyte-specific knockout of IGFR (*GFAP-Cre*^{TAM}*/igfr*$^{f/f}$*).* The impact of IGF-1 signaling on mitochondrial function was evaluated in hippocampus of LID mice and in primary astrocyte cultures from *igfr*$^{f/f}$ mice using AAV-Cre mediated knockdown using Oroboros respirometry and Seahorse assays.
Results: We show that decline in hippocampal-dependent spatial learning with age is associated with increased gliosis reduced IGF-1 receptor (IGFR) expression in the hippocampus. Reducing circulating IGF-1 levels (LID mice) significantly impaired hippocampal-dependent spatial acquisition/consolidation as well as extinction (involves development of a new and competing memory trace) in male mice. These behavioral data correlated with a decline in both brain ATP levels and hippocampal mitochondrial OXPHOS coupling efficiency. Furthermore, IGF-1 deficiency increased hippocampal oxidative stress and stress-related gene expression. Astrocyte-specific knockout of IGFR also induced impairments in working memory and reduced anxiety compared to controls. Using primary astrocyte cultures, we show that reducing IGF-1 signaling via a 30-50% reduction IGFR expression, comparable to the physiological changes in IGF-1 that occur with age, significantly impaired ATP synthesis. IGFR deficient astrocytes also displayed altered mitochondrial structure and function and increased mitochondrial ROS production associated with the induction of an antioxidant response. Moreover, IGFR deficient astrocytes also showed significantly impaired glucose and Aβ uptake, both critical functions of astrocytes in the brain.
Conclusions: Regulation of mitochondrial function and redox status by IGF-1 is essential to maintain astrocytic function and coordinate hippocampal-dependent spatial learning.
Relevance to Allied Health: Decline in IGF-1 signaling may contribute to many of the central and peripheral dysfunctions associated with age including increased susceptibility for the development and progression of Alzheimer's disease and other age-associated cognitive pathologies.