Metabolism and Redox Signaling in Brain Aging and Neurodegeneration

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Deficits in glucose availability, mitochondrial function, and inflammatory responses are well-known hallmarks of the aging brain and are particularly accentuated in neurodegenerative disorders, such as Alzheimer's disease. The decrease in energy metabolism associated with brain aging may be assessed in terms of a coordinated metabolic triad encompassed by mitochondria, insulin signaling (IKIS), and JNK (c-Jun N-terminal kinase) signaling. Impairment of these coordinated responses leads to the cognitive decline that occurs with aging and neurodegenerative disorders. The complexity of the antagonism and cross-talk between IIS- and JNK signaling and how they converge on mitochondrial function underscores the significance of an insulin resistance state. Moreover, diabetes and obesity are considered risk factors to the brain hypometabolic state, thus placing insulin resistance as a major driver that coordinates the development of these insufficiencies. The hypometabolic state inherent in brain aging and a mouse model of Alzheimer's disease is accompanied by decreased brain glucose uptake, an imbalance between IIS- and JNK signaling, decreased rate of glycolysis and flux of metabolites to the TCA cycle, and diminished synaptic plasticity. These effects are not cell specific because astrocytes developed an age-dependent energy phenotype (increased mitochondrial oxidative metabolism and biogenesis) and augmented responses to inflammatory cytokines. Multiple mechanisms account for the bioenergetics deficits and microglia activation as the driving forces that contribute to cognitive decline during aging. Brain mitochondrial H_2O_2 –through thiol/disulfide exchange mechanisms– serves as a link between bioenergetics and neuroinflammation, the latter entailing NFkB signaling and inflammasome assembly and activation.