Brain Aging and the Liver-Brain Axis

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A mitochondrion-centric approach to brain aging and the liver-brain axis entails the coordination of signaling pathways that lead to impairment of brain function and cognitive decline by a regulatory devise affecting the mitochondrial energy-redox axis, JNK, and insulin signaling. Brain aging was associated with decreases in insulin receptor and insulin receptor substrate (IRS) and PI3K/Akt signaling pathway and with increased activation JNK, the latter promoting the inhibition of the IRS. Mitochondrion-released H_2O_2 led to the activation of JNK and its translocation to the outer mitochondrial membrane, where it triggered the inhibition of pyruvate dehydrogenase with concomitant decline in ATP production, increase of lactate and reduced mitochondrial biogenesis. The liver-brain axis was monitored with two mouse models consisting of high-fat diet (HFD) and a PTEN deletion. The former induced hepatic insulin resistance, decreased mitochondrial biogenesis and insulin signaling, resulted in the activation of inflammatory responses, diminished brain glucose uptake and insulin-sensitive neuronal glucose transporters and impaired brain insulin signaling. This coincided with a decrease in learning and memory. The hypermetabolic state observed in the brains of HFD mice was the result of increased astrocytic metabolic activity, to meet the energetics demands of the insulin-resistance neurons. Conversely, in the liver-specific *Pten* null a decreased of insulin levels and increased glucose clearance rate was observed. Dynamic PET imaging showed that brain insulin sensitivity improved glucose uptake and ^{13}C NMR data revealed an amplified metabolite flux. It can be surmised that HFD amplified brain insulin resistance and diminished long-term potentiation whereas the *Pten* null mouse model proceeded with an intensification brain insulin sensitivity and augmented long-term potentiation.